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14. ABSTRACT The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). In the first year the consortium solicited proposals through an RFA and selected four research studies for further development and funding. The consortium also developed a Manual of Operations, an Intellectual Property Agreement, a fully operational website with private and public access, and fully executed subcontracts between all consortium leadership partners. In tandem with the development of the four studies selected from the first RFA, the consortium developed a second draft RFA and a plan for distribution to solicit a Phase II clinical trial.					
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1. Introduction

The goal of the PASA Consortium is to fund research that aims to identify and develop new medications to improve treatment outcomes for alcohol and substance use disorders (ASUD), especially those that occur concurrently with traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD). Clinical trials that include military service member and Veteran populations are highly desirable because this comorbidity, along with mild to moderate TBI, is common in these populations. Alcohol use disorder (AUD) is the most common ASUD in the military, but opiate use disorder (OUD) also has developed significant clinical importance due to prolonged pain treatments with opiates. FDA approved pharmacotherapies are available for ASUD, OUD, and PTSD. While TBI is of interest, it has no FDA approved specific pharmacotherapies, and none of these combined disorders have FDA approved pharmacotherapies. Under a Cooperative Agreement, RTI International is partnering with the CDMRP to solicit, select, and operationalize research studies that support the goals of the PASA Consortium.

The PASA Consortium has three aims under the primary objective to develop medications to treat ASUD in the context of the reciprocal relationship between ASUD, the physiological state of stress, and the subjective state of anxiety as manifested in PTSD or TBI. The three broad aims are:

AIM 1. Discover novel medications and combination medications for ASUD

AIM 2. Develop these medications through a rational Phase I proof of concept pipeline

AIM 3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications

2. Keywords

alcohol and substance use disorders
post-traumatic stress disorder
traumatic brain injury
request for applications
pharmacotherapy
research consortium

3. Accomplishments

- a. What were the major goals and objectives?
- b. What was accomplished under these goals? Major activities, specific objectives, significant results or key outcomes, other achievements. Discuss goals not met. Include pertinent data and graphs.

Our primary objectives for the first year was to identify scientifically sound pre-clinical studies and human clinical trials to be developed, supported, and managed through the PASA Consortium infrastructure, and to complete all administrative deliverables outlined in the notice of award.

To begin the process of study selection, we first released a Request for Pre-Applications on November 16 that outlined the application procedures and the elements critical to consideration for award. We received 13 applications in response to the request and selected 5 for GSC review and approval to submit full applications. The five applications netted four studies (2 Discovery and 2 Proof of Concept) as described below.

3.1 Discovery Studies

3.1.1 “Assessing pharmacotherapies in animal models of post-traumatic stress disorder and alcohol use disorder” (Principal Investigators: Drs. Colin N. Haile, Therese A. Kosten)

The primary objective of this study is to test the efficacy of 2 anti-hypertensive drugs (both of which target norepinephrine) and one kappa opioid antagonist in reducing PTSD-induced alcohol intake in a rodent model of PTSD/AUD comorbidity. The study has three aims to support this objective:

Aim 1 will make use of a clinically-relevant model of PTSD in rats to determine the ability of candesartan, perindopril and CERC-501 to reduce PTSD symptoms. The hypothesis is that all of the drugs will decrease PTSD symptoms.

Aim 2 is about testing the ability of candesartan and perindopril to reduce alcohol self-administration. The hypothesis is that the drugs will reduce drinking.

Aim 3 will determine the ability of the drugs alone or in combination to reduce PTSD-induced alcohol drinking. The hypothesis is that the drugs alone will reduce PTSD-induced drinking and that drug combinations will be even more efficacious.

This study was selected for its alignment with the PASA Discovery aim to develop effective drug therapies for comorbid PTSD/AUD. The strengths of the study include (1) the proposed PTSD model in that, similar to humans exposed to traumatic stress, only a subset of rats that are exposed demonstrate enduring PTSD-like symptoms, representing a vulnerable population and (2) behaviors other than amount of alcohol consumed will be examined, such as anxiety-like behavior, sensitivity to pain and avoidance of an aversive stimulus all of which mirror human symptoms of PTSD.

3.1.2 “Preclinical Analysis of Combined Carisbamate and Doxazosin Treatments in Stress---Alcohol Drinking Models” (Principal Investigator: Dr. Howard C. Becker)

The primary objective of this study is to test the efficacy of carisbamate and doxazosin (independently or in combination) on a) stress-induced alcohol drinking and b) PTSD-induced alcohol drinking. The study has two aims to support this objective:

Aim 1: Determine effects of carisbamate and doxazosin treatments, alone or in combination, on stress-induced drinking in dependent and non-dependent male and female mice.

Aim 2: Determine effects of carisbamate and doxazosin treatments, alone or in combination, on PTSD-induced drinking in dependent and non-dependent male and female mice.

This study was selected for its alignment with the PASA Discovery aim to develop effective drug therapies for the synergistic effects of PTSD and AUD. Given that comorbid PTSD and AUD represent more than just a combination of 2 disorders in that PTSD confers risk for development of AUD and AUD interferes with PTSD treatment, it is important to pre-clinically test drugs that may treat PTSD/AUD comorbidity. It proposes to test 2 drugs that have shown efficacy in treating either PTSD or AUD in humans (but not comorbid PTSD/AUD), with consideration to how the two drugs may act in combination with each other (eg., additively, synergistically or antagonistically). If the drugs prove efficacious in this preclinical study (either alone or in combination), it would indicate the need for clinical trials in populations with AUD/PTSD comorbidity.

3.2 Proof of Concept Studies

3.2.1 “Efficacy and Safety Study of ORG 34517 in Veterans with Co-morbid PTSD/AUD”

(Principal Investigator: Dewleen G. Baker, MD)

The primary objective of this study is to test the efficacy, safety, and tolerability of a novel GR antagonist (ORG 34517) for AUD/PTSD dual diagnosis treatment in veterans. The study has two aims to support this objective:

Aim 1 is to evaluate ORG 34517 treatment compared to placebo taken over 14-days of active treatment, followed by 14 treatment-free days in veterans with co-occurring AUD/PTSD. The hypotheses are (a) extinction recall at 14 days after initiation of treatment will improve, (b) subjectively rated PTSD symptoms, alcohol craving and alcohol consumption at 28 days after initiation of treatment will be reduced; and (c) the treatment will be safe and well tolerated.

Aim 2 is to evaluate the safety of study drug ORG 34517 taken concurrently with alcohol consumption, in 10 non-treatment seeking AUD subjects by evaluating safety endpoints (vital signs, laboratory measures, AEs) during alcohol challenge prior to, and after 4 days of ORG 34517 treatment, when ORG 34517 has reached steady state. The hypothesis is that the drug will be safe and well tolerated.

The study aligns with PASA aims for a proof of concept study to assess safety and surrogate markers (extinction learning) of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. The medication is novel and innovative, and the mechanism of action (GR antagonism) for treatment of the key symptoms/behaviors is supported by previous research, including two clinical trials currently underway (PTSD in veterans, AUD is non-veterans) using a drug with a similar mechanism of action. The efficacy is likely via modulation of the stress-axis, which is a logical target for the PTSD+AUD population.

The study team and the PASA leadership jointly decided to remove Aim 2 as a component of this study and consider it as a separate study. The Aim 2 study, named “The Alcohol Interaction Study”, will be conducted jointly between Dr. Baker and Dr. Verrico at the Baylor College of Medicine and will be completed before Dr. Verrico’s study or the Aim 1 portion of Dr. Baker’s study are initiated.

3.2.2 “Carisbamate as a New Treatment for PTSD & Co-Occurring AUD” (Principal Investigators: Drs. Christopher Verrico and Thomas Newton)

The objective of this study is to determine the safety and potential efficacy of carisbamate [300mg, twice daily] for treating PTSD and AUD symptoms in Veterans with PTSD and co-occurring AUD.

The study aligns with PASA aims for a proof of concept study to assess safety and surrogate markers of clinical efficacy in PTSD for treatment with an existing drug compound in veterans with AUD combined with PTSD. It is a short term clinical with outcomes including PTSD severity and alcohol use. There is ample safety data for carisbamate including its interactions with alcohol, and it has a similar therapeutic profile to FDA-approved Topiramate, but with a superior safety profile and longer half-life. The outcome measures are well justified and well validated (if not gold standard) with the populations (PTSD, AUD), and the inclusion of many PhenX toolkit measures is a methodological strength.

Supporting the feasibility of the study are the investigator’s established relationship with the study drug manufacturer, the existence of an IND plan, and the density of the veteran population in the greater Houston area and the study teams’ existing roles within Houston VA system. Furthermore, recruitment plans are clearly detailed and the research team has an established recruitment record in conducting studies of this type with veterans.

Not having the risk of uncovering AE’s during Phase I interaction experiments gives it an advantage for moving forward to larger trials and eventual deployment (further down the pipeline). If successful, this study would provide valuable safety and efficacy data for planning future studies of carisbamate for treatment of AUD and PTSD.

3.3 Administrative Deliverables

We finalized all deliverables outlined in the notice of award; the Manual of Operations, an Intellectual Property Management Plan, and fully executed subcontracts between our partners at Baylor University and USUHS.

We also developed a fully operational website for the consortium (<https://pasa.rti.org/>) with content about the consortium infrastructure, planned research studies, and substance abuse resources as well as functionality for member communication. The website has a public face and a private portal accessible only by those who have been granted a user name and password by the RTI webmaster.

Once the study selection process was complete we began the subcontracting and study launch process for the selected proposals. We anticipate having the subcontracts in place in the first quarter of Year 2.

- c. What opportunities for training and professional development did the project provide?

Nothing to Report

- d. How were the results disseminated to communities of interest?

Nothing to Report

- e. What do you plan to do during the next reporting period to accomplish the goals and objectives?

- We will finalize the research protocols for the four studies selected by the GSC in Year 1.
- We will open all four studies and begin patient recruitment and animal testing according to schedule.
- We will monitor study progress and site performance and make adjustments to protocols, budgets, and contracts as needed.
- We will issue another request for applications for a large Phase II human study and conduct all subsequent related activities including proposal review, proposal selection, and subsequent protocol development and study launch.
- We will begin exploring data analysis and publication opportunities according to the consortium publication policy.

4. Impact

- a. This component is used to describe ways in which the work, findings and specific products of the project have had an impact during this reporting period. Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come as a result of the project relative to:
- i. The development of the principal disciplines of the project: Nothing to report
 - ii. Other disciplines: Nothing to report
 - iii. Technology transfer; Nothing to report
 - iv. Or society behind science and technology Nothing to report

5. Changes/Problems

Nothing to Report

6. Products

In the first year, the following products were developed

- (1) PASA Consortium website: <https://pasa.rti.org/>
- (2) PASA Consortium Manual of Operations (Appendix)
- (3) PASA Consortium Intellectual Property Management Plan

7. Participants and Other Collaborating Organizations

- a. What individuals have worked on the project?

Name	Project Role	Person Months	Contribution to Project
Williams, Rick L	Principal Investigator	3	Monitored progress on the PASA Study Research Planning Program (SRPP) for the 1st RFA. Reviewed applications and peer-reviews. Oversaw Management Core internal programmatic review of applications that determined recommendations for funding. Prepared funding implications overview associated with recommendations. Oversaw preparations for the 17 June 2016 GSC. Conducted primary presentation of Consortium progress and application funding recommendations to the GSC. Attended weekly meetings to manage overall Consortium progress.
Kosten, Thomas	Co-Principal Investigator	3	Attended weekly meetings. Reviewed SOS and MOO documents. Met with RFA respondents via teleconference. Reviewed and edited RFA #2. Attended GSC meeting. Discussed collaborations on funding for PASA with DoD, NIH and VA leadership.
Bradley, Lauren	Public Health Analyst	1	Protocol development for all studies, Assisted with ACURO approvals, CRF development, Wrote project summaries for website
Collins, Doreen	Consortium Clinical Research Manager	2	Developed, finalized and published PASA Consortium operations manual. Managed staff levels on key Year 1 deliverables and activities including RFA 1, proposal reviews, and protocol development of selected studies. Led weekly leadership meetings. Developed quarterly reports. Monitored spending and participated in budget planning. Facilitated development of intellectual property agreement.
Nelson, Jessica	Project Manager	1	Drafted RFA 1. Assisted with planning meetings. Managed RFA 1 email communications. Tracked RFA 1 submissions.
Nolen, Tracy	Senior Research Statistician	2	Assisted with drafting RFA 1 and RFA 2. Reviewed proposals and protocols and selected studies.
Riggs, Callie	Project Administration Specialist	1	Attended biweekly project meetings. Developed quarterly reports and annual report. Managed subcontract requests. Reviewed invoices for accuracy.

- b.** Has there been a change in the other active support of the PD/PIs or senior/key personnel since the last reporting period?

There have been no changes since the last reporting period.

- c.** What other organizations have been involved as partners?

Baylor University, as per Proposal and Contract Award.

In Year 1, we began discussions with the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and US Department of Veterans Affairs (VA) about their level of involvement in the second round of study selection and support that will occur in year 2. For the Year 2 studies, NIAA and the VA will provide consultation, guidance and expertise on the design, conduct and analysis of relevant clinical studies evaluating potential medications for treatment of PTSD-Alcohol Use Disorders. In addition, depending on the relevance of the proposed studies to the current medication development goals of the NIAAA and VA and on the availability of funds, the NIAAA and VA will consider contributing support to responsive, meritorious application(s). For example, the NIAAA might consider expanding the populations being studied beyond Service Members and Veterans by funding additional civilian sites. Similarly, the VA might consider expanding the number of VA sites by funding those sites to provide more subjects for comparisons involving behavioral interventions such as progressive exposure therapy or active medications such as to paroxetine.

In addition depending on relevance to its goals, NIAAA will evaluate supporting highly meritorious proposals that are not able to be supported by PASA for reasons of direct military relevance or limitation of funds. The second RFA allows for a one page description of an expanded design that would involve more subjects or costs in order to address known interests of NIAAA or the VA.

We will provide details of the outcomes of these collaborations as they occur in Year 2.

DoD Alcohol and Substance Abuse Consortium Award

Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

PI: Rick Williams, PhD & Thomas Kosten, MD

Org: RTI International



Study Research Planning Program RFA #1 – Aims 1 and 2

- Discover novel medications and combination medications for ASUD.
- Develop medications through a Phase I proof of concept pipeline.

Study Research Planning Program RFA #2 – Aim 3

- Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in PTSD & TBI target populations and explore functional genetic polymorphisms for matching patients to medications.



The SRPP RFA process netted 14 applications, of which 5 were invited to submit full applications. Four proposals, two clinical and two preclinical were recommended for funding based on scientific merit and alignment with consortium programmatic objectives.

Timeline and Cost

Activities	Q1	Q2	Q3	Q4
Consortium Set Up: MOP and Website				
Study Solicitation and Selection				
Protocol Development				
Launch Subcontracting Process				
Estimated Budget (\$K)	75	100	135	250

YR1 Completed Objectives

- Develop and release the first SRPP RFA for the consortium
- Complete the application review and selection process for the first SRPP RFA
- Finalize the Intellectual Property Management Plan
- Enhance the functionality and content of the consortium website
- Develop the consortium Manual of Procedures
- Work with investigators selected through the SRPP to develop complete research protocols

YR1 Objectives in Progress

- Begin the subcontracting and study launch process for the selected proposals
- Finalize research protocols for selected studies
- Finalize second SRPP RFA

Appendix A

Manual of Operations

January 31, 2016

Pharmacotherapies for Alcohol and Substance Abuse Consortium (PASA)

Manual of Operations

Final 1.0

PASA Management Core

Baylor College of Medicine

RTI International

Uniformed Services University of Health Sciences

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List of Acronyms & Abbreviations

ADSM	Active Duty Service Member
AE	Adverse Event
AMA	American Medical Association
APA	American Psychological Association
CC	Consortium Committee
CDMC	Consortium Data Management Committee
CDMRP	Congressionally Directed Medical Research Program
CFR	Code of Federal Regulations
CLT	Consortium Leadership Team
CM	Clarification Memo
CMC	Consortium Management Core
CQMP	Clinical Quality Management Plan
CRF	Case Report Form
CRM	Consortium Research Manager
DoD	Department of Defense
DMC	Data Monitoring Committee
DMSC	Data Monitoring and Safety Committee
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic data collection
F&A	Facilities and Administration
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSC	Government Steering Committee
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protection Office
HSP	Human Subjects Protection
HSPB-WG	Human Subjects Protection and Bioethics Working Group
IATA	International Air Transport Association
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IoR	Investigator of Record
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LOA	Letter of Amendment

(continued)

List of Acronyms & Abbreviations (continued)

LWGs	Leadership Working Groups
MO/MM	Medical Officer/Medical Monitor
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury
NIH	National Institutes of Health
NINDS	National Institute of Neurologic Disorders
NIST	National Institute of Standards and Technology
OHRP	Office of Human Research Protections
OMB	Office of Management and Budget
OPCRO	Office for Policy in Clinical Research Operations
ORC	Office of Research Contracts
PASA	Pharmacotherapies for Alcohol and Substance Abuse
PO	Project Officer
PRP	Peer Review Program
QA	Quality assurance
QC	Quality control
RA	Regulatory Affairs
RFA	Request for Application
RTI	Research Triangle Institute
SAB	Scientific Advisory Board
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SIP	Site Implementation Plan
SMC	Study Monitoring Committee
SME	Subject matter experts
SPSMP	Study Progress and Safety Monitoring Plan
SRPP	Study Research Planning Program
TBI	traumatic brain injury
USAMRMC	United States Army Medical Research and Material Command
USUHS	Uniformed Services University of the Health Sciences
VA	Department of Veterans Affairs
WBS	work breakdown structure

1. INTRODUCTION

The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium has three aims under the primary objective of facilitating research into the development of pharmacotherapies for substance abuse in the context of the physiological response to stress and anxiety. The three broad aims are:

1. AIM 1. Discover novel medications and combination medications for substance abuse
2. AIM 2. Develop these medications through a Phase I proof of concept pipeline
3. AIM 3. Conduct Phase II preliminary safety and efficacy trials of potential medication combinations in target populations and explore functional genetic polymorphisms for matching patients to these medications

To accomplish these aims the PASA Consortium will issue requests for proposals from investigators in the relevant fields and will work with pharmaceutical company partners to focus research on compounds that are ready for further development.

This Manual of Operations outlines the procedures for PASA operations at the level of the Core Management structure.

1.1 Structure

The PASA Consortium operates under a cooperative agreement between RTI International and the Government (U.S. Army Medical Research Acquisition Activity). In partnership with sub-grantees Baylor College of Medicine and the Uniformed Services University of the Health Sciences, RTI International will execute and manage sub-awards to other institutions with expertise and infrastructure necessary to achieve the aims of the consortium. The selection of sub-grantees will be overseen by a government-appointed Government Steering Committee (GSC).

The consortium structure is:

Government Steering Committee: The GSC is chaired by a Congressionally Directed Medical Research Program (CDMRP) representative and comprises members from branches of the military and relevant government agencies.

Consortium Leadership Team (CLT): The CLT comprises the Project Director/Co-Principal Investigator and the Clinical Research Manager at RTI International, and the Co-Principal Investigator at Baylor College of Medicine.

Consortium Management Core (CMC): The CMC is made up of nine functional areas: Clinical Management, Finance and Contracts, Site and Participant Recruitment, Biostatistics, Informatics, Regulatory Affairs (RA) and Compound Development, Human Subjects Protection, and Specimen and Image Management.

Research Sites: Research sites are located at Department of Defense (DoD), Department of Veterans Affairs (VA), and academic research and treatment centers where Veterans and Service Members are recruited for and participate in research studies or where experienced investigators plan, conduct, and analyze research studies.

Scientific Leaders: Scientific Leaders are subject matter experts from Baylor College of Medicine and RTI International, and other institutions and agencies as necessary.

Data and Safety Monitoring Board: The Data and Safety Monitoring Board (DSMB) is an independent advisory group whose subject matter expertise and membership is based on recommendations from the CLT.

1.2 Role and Responsibilities

1.2.1 Government Steering Committee

The GSC approves all studies to be conducted, recommends new studies, and identifies existing and new requirements as they arise. The GSC is the overall main governing and management committee and the committee through which the DoD collaborates with the PASA Consortium. The GSC will determine all major scientific decisions, and clinical studies proposed by the CLT will proceed into the implementation stage only with the approval of the GSC.

As needed, the GSC may establish subcommittees for special purposes. The membership of such subcommittees may include members of the GSC and other investigators participating in the PASA Consortium.

1.2.2 Consortium Leadership Team

Under the leadership of the Project Director/Co-PI, the CLT will be the main body responsible for developing, executing, and managing the operations of the consortium. The CLT will: establish the policies and procedures under which the PASA Consortium will operate, make recommendations to the GSC regarding selection of research studies, and work closely with the GSC and the CDMRP representative to strategize on the direction of the consortium and the allocation of resources.

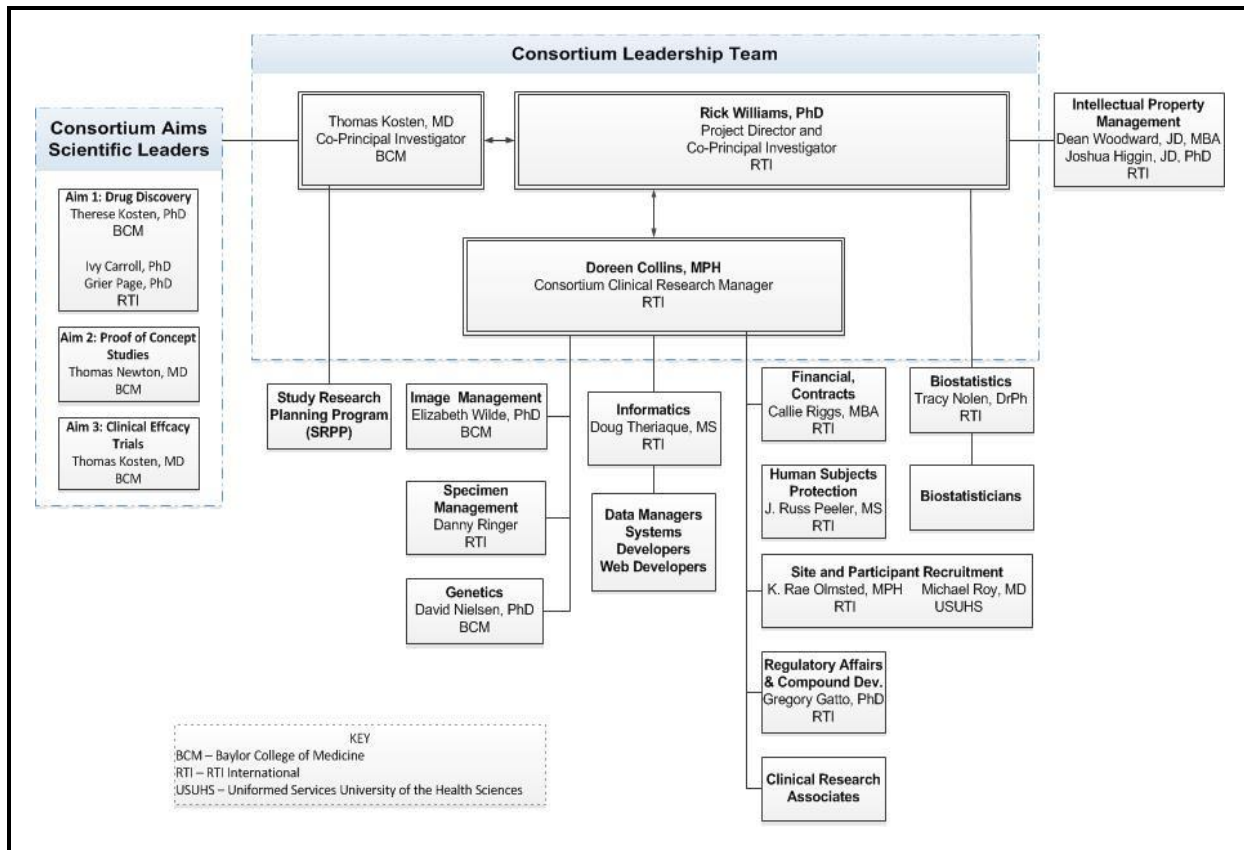
1.2.3 Consortium Management Core

The CMC functions as the operational arm under the direction of the CLT and is responsible for daily management of all aspects of the consortium. There are nine functional areas in the CMC:

Clinical Management. Under the direction of the Clinical Research Manager, the Clinical Management team coordinates protocol development and approval, study-specific training, study initiation, and study close-out. This team also ensures adequacy of subject confidentiality, informed consent procedures, and adverse event reporting through clinical site monitoring. The Clinical Management team provides input to the CLT on site performance and supervises corrective actions for underperforming sites.

Finance and Contracts. The RTI financial and subcontract manager is responsible for all subcontract administration. Subcontracts on the PASA Consortium include those between RTI and its partners Baylor College of Medicine and Uniformed Services University of the Health Sciences (USUHS), and subcontracts with recruiting sites and research labs. Subcontract administration includes monitoring of subcontractor performance and productivity, payments to clinical research sites for study activities, and consortium budget monitoring. Details of subcontract administration procedures are described in Chapter 9.

Exhibit 1. PASA Consortium Management Core



Site and Participant Recruitment. Led by Dr. Michael Roy, the Recruitment Core operates at Walter Reed National Military Medical Center, at Fort Belvoir Community Hospital and at various academic locations around Washington, DC. This team will assist in identifying and recruiting additional sites, particularly military treatment facilities (MTFs), for the conduct of clinical studies. Recruitment for Consortium-funded studies will primarily be the responsibility of the awardees. Awardees may choose, however, to solicit the assistance of the Consortium team in recruiting sites and/or study participants through the Uniformed Services University of the Health Sciences' (USUHS) Center for Neuroscience and Regenerative Medicine (CNRM) recruitment core. The CNRM has an established protocol for identifying service members (both active and reserve component), retirees, and other beneficiaries for participating in clinical research to include a database which stores preliminary data on individuals who are interested in and potentially eligible for research studies. Social media, Internet, flyers, advertisements, and informational campaigns may be used to disseminate information about study opportunities. Research Coordinators and other individuals may work within MTFs to more directly recruit potential study participants.

Biostatistics. RTI leads the biostatistics team, which provides statistical input on study design, data safety monitoring reports, and publications.

Informatics. The informatics team is based at RTI and develops secure electronic data entry systems and study case report forms, and has primary responsibility for data quality and reporting.

Regulatory Affairs and Compound Development. For certain protocols, the RA team at RTI works with the protocol team to determine whether a protocol needs Food and Drug Administration (FDA) review. If an FDA submission is required the RA team works with the sites, the sponsor (Investigational New Drug [IND] holder) and GSC to coordinate, prepare, compile, submit, and archive materials sent to FDA. This work includes preparation, formatting, and organization of an appropriate template/outline, technical and medical writing; report assembly and compilation; QC review of the package; and clinical/regulatory review.

Human Subjects Protection. As part of the study activation process, RTI will work with clinical research sites to ensure all regulatory approvals are obtained before subjects are enrolled. This team will also track site Institutional Review Board (IRB) approvals and notify sites when annual renewals are due.

Biospecimen and Image Management. Baylor College of Medicine and RTI coordinate image and biospecimen management, respectively. The biospecimen tracking at RTI is managed through a web-based software and ensures that biospecimens are accounted for at all times. The neuroimaging management at Baylor College of Medicine includes storage, transfer, and interpretation of MRI images captured at clinical research sites.

Intellectual Property Management. In partnership with Consortium members, RTI will develop an overall plan for managing intellectual property generated through research done under the PASA award. The definition of intellectual property includes patents, trademarks, copyrights, protected data, and other comparable property protected by law. The Plan will apply to all consultants, subcontractors, students, or other individuals employed under the PASA award. Individual agreements on intellectual property will be developed on a case by case basis.

1.2.4 Study Research Planning Program (SRPP)

Dr. Thomas Kosten (Baylor College of Medicine) directs the SRPP and leads the committee that will select studies for funding and explore additional resources (pharmaceutical partners) for supporting them. The committee comprises Drs. Kosten, Williams, and Carroll and three independent reviewers. The solicitation of novel concepts may occur up to three times per year through notices of funding opportunities on the PASA web site and through other research networks known to have potentially viable candidate compounds. Applicants will initially be asked to develop a one-page prospectus of the project that includes a brief description of the compound(s), hypothesized disease indication and mechanism of action, a summary of any previously conducted preclinical and clinical research, overview of plans for the proposed study, and an estimated budget range. The prospectus will be reviewed by the entire SRPP Committee and a subset of applications will be approved to develop a 10- to 20-page mini-protocol. Prospectuses will be assessed based on their:

- significance, judged on the congruence with the aims of the Consortium; and
- approach, judged on the basis of the overall scientific merit and feasibility.

1.2.5 Research Study Leadership Working Groups (LWGs)

For each study approved by the GSC, a LWG will be established to guide the operations of the corresponding study. The Study LWGs will assure that the studies are well-planned, conducted with high scientific standards, and that there is collaboration among all of the sites contributing the studies.

1.2.6 Data and Safety Monitoring Board

The DSMB is an independent advisory group that provides recommendations to the GSC based on its determinations regarding the interests of study participants, the safety and efficacy of study procedures, the quality and integrity of data, and the overall feasibility of study enrollment. The DSMB meets at least quarterly to provide oversight and monitoring of all PASA studies conducted by the PASA.

2. COMMUNICATION PLAN

The primary source of communication for critical information pertinent to the entire consortium will be the web portal. Routine communications will be managed through regularly scheduled meetings and e-mails distributed via listservs.

2.1 Web Portal

A PASA communications portal allows members immediate access to Consortium-wide information in an easily accessible Web application format. The PASA portal is the primary communication tool, providing general information to the public and private access for consortium-specific organizations and researchers to study site documents, protocols, core facility resources, Leadership Working Group material, and other resources necessary to successfully manage and operate a large multi-site/multi-study effort. The PASA website has two levels of access: a public face accessible to anyone on the Internet and a private section for registered users with the appropriate credentials and logins.

2.1.1 Public Web Access

The general public, including military personnel, potential study volunteers, and researchers interested in applying for funding can access the PASA website at <https://pasa.rti.org>. Access to the public section does not require login or membership and contains information on:

- relevant resources and links for substance abuse treatment;
- the mission, goals, leadership and governing body;
- participating organizations and Principal Investigator(s); and
- the research scope for ongoing and completed studies.

2.1.2 Private Web Access

Consortium members, including investigators, staff, and leadership with appropriate credentials login to the private section of the PASA website to access the following information:

Member Directory: A master directory of Consortium members and contacts provides all researchers with easy access to members' e-mail addresses, phone numbers, and physical addresses. The directory is dynamic and updated as changes occur.

Master Calendar: A Consortium-wide calendar provides up-to-date information on activities, scheduled meetings, and deadlines with links to meeting resources including call-in or webinar information. The PASA calendaring system is integrated with Microsoft Outlook, so meeting invitations are synchronized to ensure that any changes after a meeting is scheduled are automatically reflected both on the web calendar and on individuals' Outlook calendars.

Conference Calendar: The PASA Coordinating Center (CC) is responsible for scheduling cross-consortium meetings, teleconferences, and web conferences. A central administrative assistant has been designated as the PASA Meeting Coordinator, and will coordinate and schedule all such meetings and conferences. To facilitate telephone conference communication, the CC has provided a PASA dedicated conference line and will add more lines if needed. When individual study investigators, Leadership Working Groups, core staff or other

combinations of members arrange a conference call, the call leader (or designee) reserves the PASA conference line via the online conference line calendar. If the PASA conference line is not available, other arrangements are available for a separate conference line. In addition, web conferencing is also available and can be scheduled with the Meeting Coordinator.

Consortium Documentation: Consortium documents (e.g., protocols, study manuals, and forms) are made available to members via the website to facilitate document management including the upload of documents, version tracking, and the distribution of up-to-date document versions via e-mail links rather than attachments. Minimizing the distribution of documents via e-mail attachments provides greater document security, assists with version control and limits e-mail box clutter.

Study-Specific Areas: Consortium studies will require limited access areas (e.g., access restricted to members of the study team, RTI, and Consortium Directors) on the web portal for reports, meeting minutes, draft publications, IRB approvals, and other working documents. Requests for limited access areas are made upon initiation of a study, working group, or facility or at any time during which the group is active. The PASA portal administrator(s) works with the lead coordinator to determine which members require access, ensure that all necessary requirements have been met, and determine the appropriate role and level of access for each member.

Operational Study Management Tools: The PASA web portal allows study and Consortium leadership to monitor and direct activities using the following management tools:

- Tracking of IRB approvals and other essential documents and approvals
- Enrollment reports

The PASA website also is the central portal for data collection and capture activities. Section 8 of this manual describes these activities in greater detail.

2.2 Meetings

Meetings will generally be held by teleconference and will be arranged by the meeting attendees themselves. There will be a master calendar for all high-level regularly scheduled meetings available on the web portal. The consortium will aim to hold one in person meeting each year to allow for additional exchange of ideas and presentation of activities.

2.3 E-mail Listservs

The PASA website administrator will create listservs for core groups, study teams, and for the entire consortium. The listservs will also serve as a list of users assigned to specific role or group (e.g., protocol development team) to allow automatic access to the appropriate web portal resources. Listservs are dynamic and updated as changes occur. Consortium members can communicate with an entire group by sending an e-mail to the appropriate listserv group address. All listserv addresses use a pre-determined format.

3. STUDY RESEARCH PLANNING PROGRAM (SRPP)

3.1 Overview

The PASA Study Research Planning Program (SRPP) is designed to support the identification of preclinical studies (basic science and translational) and clinical trials to be conducted within the consortium. The process for selecting studies includes the solicitation of novel concepts and medications from both consortium and external researchers and the selection of compounds to move forward for further development after completion of previously approved studies. Dr. Thomas Kosten (Baylor College of Medicine) directs the SRPP and leads the committee that selects and prioritizes studies appropriate for funding.

3.2 Solicitations

The solicitation of novel concepts occurs at least once per year and up to two more times depending on failure versus success of previously awarded compounds or receipt of additional optional funding. Notices of funding opportunities are posted on the PASA consortium's web site and distributed to existing collaborators of Consortium investigators, pharmaceutical companies, and academic research institutes that are known to have potentially viable candidate compounds.

3.3 Applications

Novel concepts that are not primarily developed by internal PASA Consortium Investigators are assigned a Consortium Investigator to act as a champion for the concept and to work closely with the original researchers to develop the application. Applicants are asked to first develop a one-page prospectus of the project that includes a brief description of the compound(s), hypothesized disease indication and mechanism of action, a summary of any previously conducted preclinical and clinical research, overview of plans for the proposed study, and an estimated budget range. Each prospectus is reviewed by the entire SRPP Committee and a subset of applications will be approved to develop a 10- to 20-page mini-protocol.

3.4 Study Selection

The SRPP Committee assesses prospectuses based on their:

- significance, judged on the congruence with the aims of the Consortium; and
- approach, judged on the basis of the overall scientific merit and feasibility.

Each Committee member will provide a go/no-go vote and a list of any major recommendations for adjustments. All applications that receive a “go” vote from the majority will be approved. If there is significant overlap or potential for synergy between applications (e.g., employ combination therapy for two independently proposed compounds, conduct a multi-experimental arm study with multiple independently proposed compounds that are all at the same stage of development as opposed to testing each separately), the SRPP will recommend that the investigators collaborate to submit a single mini-protocol. The mini-protocol will expand on study design including aims, outcome measures, eligibility criteria, sample size estimates, analytic approach and study timeline, and must specify which sites will participate in the study and include a detailed research budget. A statistician from the CMC will be paired with the investigator to aid in study design development including conducting sample size estimates and identifying the appropriate analytic approach. The CMC will also help identify research sites for study participation and assist with the development of the research budget. The draft mini-

protocol, potential site budget, and required recruitment rate would be provided to candidate sites named by the investigator or sites already existing within the Consortium. If there is an insufficient number of interested sites that are capable of conducting the study, we will reach beyond these sites to other VAMC and military bases and the Recruitment Core to ensure that projected enrollment will allow for completion of each study in a timely manner. The final list of potential sites will be included as part of the full application. Each full application will be reviewed and scored by two members of the SRPP Committee, one of the independent reviewers and one Consortium team member who was not involved in the development of the mini-protocol.

Applications will be scored on the following factors:

1. scientific merit (e.g., medical significance, quality and appropriateness of research plan, feasibility)
2. administrative merit (e.g., reasonableness of budget, availability of necessary resources, collaboration/co-funding potential with pharmaceutical company).

The reviewers will present the scores and comments to the SRPP Committee, which will then assign an overall score for each application and make recommendations of approval, disapproval, or deferral with suggestions for revision. The SSRP leaders, Drs. Kosten, Williams, and Carroll will then compile the scores and in collaboration with the GSC make the final determination of which applications are approved for full protocol development and implementation.

3.5 Further Research—Novel Compounds

The GSC and SSRP leaders will also be responsible for determining which compounds will move forward for further development after completion of previously approved studies. For these compounds, evidence required to support the need for continued research will be incorporated into the study protocol as part of the study design and analytic plan. For example, early proof-of-concept phase I studies of multiple compounds may incorporate an adaptive design where compounds are dropped from the study because of toxicity or failure to exhibit efficacy signals and any remaining compounds at the end of the study would be intended for future research in a larger proof-of-concept phase II study. At the conclusion of each study the SSRP leaders will review the final study report and determine whether the findings support the need for additional research. If approved, the investigator will be asked to submit a mini-protocol for the next phase study. The review process of the mini-protocol will follow that described for new concepts; however, generally mini-protocols for these continuation studies will be given priority over new concepts with all final decisions for funding made by the SSRP leaders.

4. PROTOCOL DEVELOPMENT AND MAINTENANCE

4.1 Overview

After a protocol concept is approved by the SRPP selection process, the protocol PI will initiate the protocol development process. The CMC will assist the PI by providing staff with expertise in study management, data management, or biostatistics as needed. The CMC will also assign a unique number to each approved protocol concept that will be used in all correspondence for the protocol and will appear on all protocol documents.

4.2 Human Participants

4.2.1 Protocol Leadership Working Group

Depending on the completeness of the protocol at the time of application, an LWG may be formed to continue development toward implementation. The composition of the Protocol LWG is finalized by the Protocol PI with approval of the CMC and the GSC. The primary purposes of Protocol LWGs are to:

- Expand and develop approved protocols until they are in the final form;
- Modify protocols to meet the recommendations of the GSC and Data Safety Monitoring Board;
- Develop the manual of operations and data collection forms, procure equipment and supplies, and plan other logistics necessary to implement the study;
- Produce information targeted to patients or physicians and make presentations on the study design to promote recruitment at all Consortium sites;
- Advise the CMC and the GSC regarding special problems or concerns that arise during the course of study implementation or conduct;
- Propose and review primary and major secondary data analyses; and
- Prepare abstracts, make presentations and write manuscripts on the primary and major secondary study results.

Responsibility for these functions is delegated to the Protocol LWG by the GSC. The Protocol PI assumes leadership responsibility, but must collaboratively work with the other members of the LWG. Those responsibilities include: convening meetings and conference calls and monitoring the overall progress of the study. Should an area of contention arise, Protocol LWG members shall vote on the issue, with the majority vote ruling.

Protocol LWGs are composed of Consortium members who have interest and expertise in the proposed area of scientific inquiry along with members external to the Consortium selected to provide special expertise where needed. In general, each Protocol LWG will consist of the following membership:

- Protocol PI (chairperson)
- Protocol Co-Investigators representing each of the sites participating in the study and the scientific areas of investigation

- Site/Nurse Coordinator—at least one site/nurse coordinator from a site(s) participating in the study
- Two CMC Representatives—Study Manager and Lead Statistician
- Ad Hoc Subject Matter Experts

Individuals who are not part of the Consortium, yet are enlisted to participate on Protocol LWGs must have special expertise in the area of the protocol. In addition, representatives of government agencies (e.g., FDA) with relevant expertise may be enlisted to serve on Protocol LWGs. Such external members may be nominated by members of the Protocol LWG or the GSC, and must have the approval of the Protocol PI and the GSC.

4.2.2 Protocol Development Timeline

The LWG will identify a Coordinating Author who will have primary responsibility for incorporating edits, maintaining version control, and monitoring the development timeline with a Gantt chart. The Coordinating Author will create the Gantt chart in consultation with the protocol PI. The timeline on the Gantt chart must include the following items:

- Major milestones
- Conference call schedules
- Due dates for input
- Draft protocol distribution dates
- Schedule dependencies
- Critical path

The schedule must allow adequate time for all team members to review the protocol, provide written input, hold conference calls and respond in writing to issues raised during calls, compile input, and distribute protocol revisions. Guidelines for timelines are below:

- Review of first draft by collaborators and SMEs—7 to 10 business days (includes time allowed for conference calls)
- Review of first draft by PASA leadership—10 to 15 business days
- Coordinating Author compile input into next draft—2 to 3 business days
- Protocol LWG review of drafts subsequent to first draft—5 to 7 business days

The number of revisions will vary for each protocol and will depend on the level of development of the initial concept, the complexity of the protocol, and the ability of the group to come to consensus on the content.

The Protocol PI will have primary responsibility for assigning sections to authors.

4.2.3 Version Control and Master Documents

The Coordinating Author will distribute the protocol outline and instructions to the protocol authors along with the section assignments and due dates. The review and input process is as follows:

1. The Coordinating Author will assist in scheduling small group conference calls, as requested, among the authors to discuss the protocol sections and content. The dates and frequency of the calls will be determined by the small groups themselves.
2. The Coordinating Author will collate the input from the authors and assemble the first protocol draft which will be labeled as version .01. The document will be named with the date, the name of the protocol and the version number (for example, 20131125_Study1_v.01) with the document name included in a footer within the document.
3. If the input will not be available on the due date, the author will notify the Coordinating Author and provide a new due date in consultation with the committee.
4. The Coordinating Author will keep the Protocol PI apprised of all revised due dates and resulting schedule changes.
5. The Coordinating Author will distribute the .01 version of the protocol to the protocol authors and to the LWG for review and comment along with the expected review schedule. The Coordinating Author will monitor the schedule and keep the Protocol PI apprised of any revised due dates and resulting schedule changes. Corrective actions will be taken if development does not stay on schedule.
6. The Coordinating Author will incorporate all input according to the following parameters:
 - All new text will be added using tracked changes.
 - Deletions will be marked using tracked changes.
 - All comments in the margin will be added to the protocol and the author will be identified by name or by committee.
 - If there are sections of the protocol that are not yet completed, the Coordinating Author will include an outline for those sections in the protocol.
7. Once all input is incorporated into the protocol, the Coordinating Author will change the protocol version to .02, or the next incremental version number, and distribute the protocol as follows:
 - Obvious spelling, grammar and formatting errors will be corrected.
 - The title of the document will be the date (year-month-day format), protocol name, and draft version number (for example, 20131207_Study1_v.02).
 - The title of the document will be in the footer on every page.
 - The date and version number will be on the protocol cover page.
8. The Coordinating Author will save the compiled protocol document with the word TRACKED at the end, and then create a second document with all changes accepted, all comments deleted, and all highlighting removed and save the new document with the word CLEAN at the end.
9. The Coordinating Author will send both the clean and tracked versions on to the next stage of review.

4.2.4 Protocol Finalization and Distribution

The Protocol PI, with the concurrency of the Protocol LWG and the PASA leadership, will determine when the protocol is considered complete. The Coordinating Author will create a

final formatted clean document and the final protocol version will be 1.0. The protocol cover page, document title, and footer will change accordingly. The Coordinating Author will send the final version to the Protocol PI, the Protocol LWG, and to the IRB representative to begin the IRB submission process.

All documents will be distributed electronically and the final version will be posted in PDF format on the consortium website.

4.2.5 Protocol Modifications

Any protocol changes after the release of the 1.0 version will follow the same procedural process described above. Changes to the protocol will be made through the following methods:

1. Clarification Memos
2. Letters of Amendment
3. Full Version Protocol Changes

4.2.5.1 Protocol Clarification Memo

A Protocol Clarification Memo (CM) is used to provide additional detail or further explanation to information that is already included in the protocol. Sites are not required to submit Clarification Memos to their IRBs unless the site IRB indicates otherwise. A CM does not affect participant safety or the risk assessment of the protocol and does not change the Informed Consent Form (ICF).

The following examples are instances in which a CM would be the appropriate method for implementing a clarification to a protocol:

- Updates or corrections to phone numbers or addresses for protocol team members/laboratories already listed in the protocol.
- To correct inconsistent information in the protocol (e.g., the schedule of events specifies a lab test or blood volume to be collected at a specific study visit and conflicting information is included in the corresponding section of the protocol document).
- To specify a specific type of collection tube to be used for drawing a lab specimen.

4.2.5.2 Letters of Amendment (LoA)

An LoA can be used when there are specific changes to the protocol that result in the addition of new information or the deletion of incorrect or unnecessary information. The PASA requires that sites submit LoAs to the local IRB for review and approval prior to their implementation. An LoA may result in minor changes to the ICF.

If the collective changes being requested by the protocol team are extensive and cannot be implemented easily and immediately, or if multiple LoAs have been implemented for a single version of the protocol and additional changes are requested, the PASA leadership may require the Protocol LWG to develop a Full Version Protocol Amendment.

The following examples are instances in which a LoA would be the appropriate method to make changes to a protocol:

- Changes to the volume of blood or number of samples that will be collected at a specific study visit.

- Changes to the procedures or lab tests that will be conducted at a specific study visit. Any new lab test or procedure should not increase the risk to the participants. The addition of a blood draw would be acceptable while the addition of a lumbar puncture would require a Full Version Protocol Amendment.
- A change to the inclusion/exclusion criteria that results in slightly broadening parameters to help increase enrollment (e.g., expanding the range of time for eligibility).
- A change in the schedule of study product dosing which results in a lower dosage being given or a reduction in the frequency in which study product is given.
- The dropping of a protocol arm based on the recommendation of the DSMB which does not affect the other arms.

4.2.5.3 Full Version Changes

A full version protocol amendment is utilized when required changes to a protocol are substantive in number or nature. A full version protocol amendment results in a new protocol version number (e.g., Version 2.0, 3.0). Protocol changes made via a Full Version Protocol Amendment are incorporated directly into the protocol document. A Full Version Protocol Amendment must incorporate all CMs and LoAs previously implemented since the last approved version of the protocol. Full version protocol amendments must be reviewed and approved by the site IRBs before being implemented.

The following examples would require a Full Version Protocol Amendment:

- The protocol PI/Committee/LWG has identified major issues that require changes to the protocol.
- An increase or decrease of more than 10% of the total number of participants to be enrolled.
- Any change which results in a change to the protocol design that includes but is not limited to:
 - Inclusion of a new sub-study
 - Inclusion of a new informed consent form or significant changes to the existing form.
 - A change in the schedule of study product dosing which results in a higher dosage being given or an increase in the frequency in which study product is given.
 - The introduction of a new study product or study product formulation.

4.3 Animal Studies

All animal studies conducted as part of the PASA consortium will require an animal protocol describing the technical aspects of the study. This protocol will be drafted by the team conducting the study and will be reviewed and approved by the study Leadership Working Group members and the Consortium Leadership. Upon e-mail approval from all members of the LWG and PASA leadership, the protocol is considered final and the study can officially begin. The final protocol must be sent to the CMC, where it will be maintained as a controlled document. All protocol deviations and amendments that occur during the course of the study

must also be documented in similar fashion, reviewed by the LWG and PASA Leadership, and sent to the CMC to be stored with the original protocol.

Guidance for best practice in the development of an animal study protocol comes from U.S. FDA Good Laboratory Practices (or similar guidance from U.S. Environmental Protection Agency or Organisation for Economic Co-operation and Development). Good Laboratory Practices are typically applied to regulatory guideline animal toxicology studies, but the basic elements for a research protocol are the same.

Also, guidance for best practice in the development of an animal study protocol is discussed by several government agencies relevant to PASA studies: VA, DoD, and the Army. See any of the three links below as additional guidance documents.

VA: VHA Handbook on use of animals in research (2011):

http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2464

DoD: Animal Use (DoD Standard Animal Use Protocol Format):

http://www.dtic.mil/biosys/docs/au-DoD_Standard_Animal_Use_Protocol.pdf

Army: Animal Use Appendix for Research Involving Animals:

http://mrhc.amedd.army.mil/index.cfm?pageid=research_protections.acuro_animalappendix

5. REGULATORY OVERSIGHT

5.1 Regulatory Approvals

PASA protocols that involve human subjects must receive full approval from the clinical site IRB(s) and from the U.S. Army Medical Department Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protection Office (HRPO) before study participants can be enrolled. Regulatory approvals may also be required from the Veterans Health Administration and the FDA. When appropriate, protocols may be approved by a central IRB of record to streamline the IRB approval process.

The PASA leadership will collaborate with the GSC to determine whether multiple IRB reviews are necessary, or whether one organization may be allowed to serve as the central IRB of record.

PASA protocols that involve testing on animals must be reviewed and approved by the USAMRMC ORP Animal Care and Use Review Office (ACURO) before research can begin. Each animal protocol must include (1) a justification for using animals, the number of animals to be used, and the species chosen, (2) the procedures or drugs to be used to eliminate or minimize pain and discomfort, (3) a description of the methods and sources used to search for alternatives to painful procedures, and (4) a description of the search used to ensure that the experiment does not unnecessarily duplicate previous research.

5.1.1 Approval Process – Human Studies

The CMC will send the final draft version of the protocol to the appropriate points of contact at the DoD for a pre-review. The purpose of the pre-review is to solicit feedback on any regulatory or human subject's protection issues in a protocol and the informed consent and to refine and clarify language in preparation for IRB review.

The CMC and the protocol PI will address the pre-review edits and issue the first final version of the protocol. Once the protocol is finalized the CMC will distribute the protocol and the informed consent form to the clinical research sites for submission to the IRB(s) of record.

If a central IRB will be used for the protocol, the CMC will coordinate the preparation of all necessary protocol documents for submission to the IRBs of record. If individual institutions choose not to accept the centralized IRB review model and require separate submissions, the CMC will work with consortium members to amend the centralized documents to fit the needs of those individual IRBs and coordinate their submission and approval.

Once a site's IRB has approved the protocol, the CMC will submit the protocol along with the IRB approval to HRPO. The CMC will coordinate communication between HRPO, the clinical site staff, the protocol PI and LWG, and PASA Leadership as needed to obtain HRPO approval. Once HRPO issues an approval for the protocol, the CMC will notify the relevant consortium members and, if all other required documents are in order (see Chapter 7 "Site Activation"), the site may open the study to enrollment.

5.1.2 Approval Process – Animal Studies

As with human studies, the CMC will send the final draft version of the protocol to the appropriate points of contact at the DoD for a pre-review. The purpose of the pre-review is to solicit feedback on any animal care and use issues in a protocol in preparation for animal use committee review.

The CMC and the protocol PI will address the pre-review edits and issue the first final version of the protocol. Once the protocol is finalized the CMC will distribute the protocol and research sites for submission to the site's animal care and use committee for review.

Once a site's committee has approved the protocol, the CMC will submit the protocol along with the site committee approval to ACURO. The CMC will coordinate communication between ACURO, the research site staff, the protocol PI and LWG, and PASA Leadership as needed to obtain ACURO approval. Once ACURO issues an approval for the protocol, the CMC will notify the relevant consortium members and the site may begin the research study.

5.2 Protection of Human Subjects

The Federal Policy for the Protection of Human Subjects or the "Common Rule" was published in 1991 and codified in separate regulations by 15 Federal departments and agencies, including the Department of Defense and the Department of Veterans Affairs. Each agency includes in its chapter of the Code of Federal Regulations [CFR] section numbers and language that outline the basic provisions for IRBs, informed consent, and Assurances of Compliance. Human subject research conducted or supported by the Department of Defense and the Department of Veterans Affairs is governed by the regulations of each respective department. The head of that department retains final judgment as to whether a particular activity it conducts or supports is covered by the Common Rule.

The applicable CFR numbers for the activities conducted under the PASA are: 32 CFR Part 219 (Department of Defense) and 38 CFR Part 16 (Department of Veterans Affairs). Additional regulations under the Food and Drug Administration's CFR chapters will apply for investigational drug studies conducted under the PASA.

5.3 Clinical Site IRB Review

For multisite studies in which each site's IRB is reviewing the protocol, a site may begin enrollment once its own IRB and HRPO have approved the protocol, regardless of the status of the reviews at other sites. However, a local site IRB may override this policy and disallow its site from opening enrollment until all IRBs have reviewed the protocol.

A site's IRB may make protocol approval contingent upon changes to the protocol or the informed consent form. Minor editorial changes to the consent form can be made without further review from the PASA leadership. If the IRB requests changes to the protocol, the site staff will forward the IRB's request to the CMC, which will review the issue with the protocol PI, HRPO, and the Consortium leaders. If the Consortium leadership does not approve the IRB's request, the protocol will not be opened at the site.

Site staffs must obtain continuing review and approval of the consent form and protocol from their IRBs annually and forward documentation of the annual renewal to the CMC. If there is a lapse in IRB approval, a site cannot enroll subjects or conduct study procedures until the IRB has conducted its annual review.

5.4 Informed Consent

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The research staff must obtain consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language

understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

The informed consent form must have a current (unexpired) IRB approval stamp or other mark indicating IRB review and approval. The date of the participant's or the representative's signature must be written by the signatory him/herself and not by the research staff. The research staff person who reviewed the consent form with the participant must also sign and date the form and the dates of both signatures must be identical. Research staffs may not in any way change, mark up, obliterate, or add text to the consent form. After signing the form, the participant must be offered a copy of the form and the form with the original signatures will remain in the study files. Informed consent must be obtained before any study procedures are conducted.

Study staff must write a brief narrative in the participant's research file outlining the informed consent process. Minimal elements of the narrative include:

- Persons present during the process
- The participant verbalized understanding of the risks, schedule, and aims of the study
- The participant's questions, if any, were answered
- The participant was offered a copy of the consent form

If any language in the consent form is changed during the course of the study, all participants currently on-study must sign the new IRB-approved informed consent form. Participants do not need to sign the informed consent forms again after IRB continuing review if no changes have been made.

5.5 HIPAA Rule and Participant Authorization

The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule establishes the conditions under which protected health information may be used or disclosed for research purposes. Research is defined in the Privacy Rule as, "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." See 45 CFR 164.501.

All PASA research study participants will be asked to provide written authorization to use and disclose health information for each research study. The clinical sites will be responsible for developing the HIPAA form specific to their institutions. The HIPAA authorization must be signed during the informed consent process, and a participant cannot be enrolled in the study without a signed form.

5.6 Adverse Event Reporting

The PASA consortium will conduct Phase I and Phase II research protocols, which are generally considered to be greater than minimal risk. For these types of studies, sites are required to collect data on adverse events (AEs) and serious adverse events (SAEs) and to report these events to the regulatory authorities and to the CMC.

In general, SAEs will be reviewed by the regulatory agencies that are relevant to a particular study. These may include a medical safety monitor, the sponsor (DoD), DMC, FDA, and site IRBs.

SAEs that are deemed *related* to the intervention and *unexpected* will be reported in an expedited manner to the above relevant regulatory agencies.

a. Grading Adverse Events

AEs will be rated as mild, moderate, or severe according to the following definitions:

- Mild—No interruption in daily activities/No therapy
- Moderate—Short interruption in daily activities/May require therapy
- Severe—Significant interruption of daily activities/Therapy required

If an AE does not clearly fit into one of the above categories, the study PI or treating physician should use their medical expertise to make the determination of severity.

b. Assigning relationship to study intervention

The AE's relationship to the study drug, device, or procedure will be determined by the principal investigator (PI) at the site according to the following options:

- Definitely not related
- Possibly related
- Probably related
- Definitely related

A related AE or a related problem in DoD (specific to military component) research is an AE or problem that may reasonably be regarded as caused by, or probably caused by, the research.

c. Determining expectedness

The terms unanticipated and unexpected refer to an event or problem that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

d. Serious¹ adverse events

Untoward physical or psychological occurrence in human subject participating in research that results in:

- Death
- Congenital anomaly/birth defect in a fetus or newborn
- Inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability or incapacity

¹ Please note: The term "severe" used to grade intensity is not synonymous with the term "serious."

- Life-threatening experience²
- An AE that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome³

5.7 Financial Disclosure Form

U.S. regulations, 21 CFR 321.53 and 21 CFR 812.43, state that before an investigator is allowed to begin an investigation, the IND/Investigational Device Exemption (IDE) sponsor shall obtain sufficient, accurate financial information that will allow an applicant of a marketing application to submit complete and accurate certification or disclosure statements as required under 21 CFR 54. Per the FDA Guidance regarding Financial Disclosure by Clinical Investigators, the IND/IDE holder, even if not the applicant filing the marketing application, is required to collect financial information before permitting an investigator to participate in a clinical study. Each clinical investigator who is participating in a study that could be used to support a marketing application must submit either a completed financial disclosure statement attesting to the absence of financial interests/arrangement or disclosing any financial interests/arrangements or steps taken to minimize the potential for bias.

PASA will request confirmation that financial disclosure forms/statements are completed by all investigators listed for any PASA sponsored or supported study where PASA is the IND holder.

5.8 Essential Documents

Essential Documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The documents required during the lifecycle of a clinical investigation are not clearly described in the Federal regulations governing recordkeeping and record retention (21 CFR 312.62 and 812.140). However, the FDA has adopted the International Committee on Harmonisation's E6 consolidation guide for Good Clinical Practices (GCPs) definition, Section 8, as its guidance document on this topic. Essential documents are used for the following purposes: (1) to demonstrate the compliance of the investigator, sponsor, and the monitor with all applicable regulatory requirements and GCP, (2) to assist in the successful management of the study by the investigator, sponsor, and monitor, and (3) to confirm the validity of the conduct of the clinical investigation and the integrity of the data collected.

The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both.

Master study files must be established at the beginning of the study, both at the investigator's site and at the sponsor's office. A final close-out of the study can be done only after a monitor has reviewed both the investigator files and the sponsor files and confirmed that all necessary documents are in the appropriate files.

² Life-threatening means that the study patient was, in the opinion of the principal investigator, at immediate risk of death from the event as it occurred.

³ An important medical event is any medical event that may not qualify for other categories, but may jeopardize the health of the study participant or may require medical or surgical intervention to prevent one of the outcomes listed above.

All the essential documents are subject to audit by the PASA, sponsor's auditor and inspection by regulatory agencies.

Appendix B is a sample list of essential documents.

5.9 Clinical Trial Registration

The Food and Drug Administration Modernization Act and the Food and Drug Administration Amendments Act mandate public registration of certain types of clinical trials. Failure to comply with these legal requirements may result in administrative sanctions and civil penalties and, when applicable, withholding or even possible repayment of Federal funding.

On behalf of the sponsor or principal investigator, the CMC will register all eligible PASA clinical trials in clinicaltrials.gov. The CMC will review and update PASA trial information twice a year. Failure to register a clinical trial may result in project delays or termination by a funding agency or even recovery of funds from funding agencies and inability to publish results.

5.10 IND and IDE Filing

Prior to filing an IND/IDE, a pre-IND or pre-IDE (known as pre-Submission) meeting with appropriate representatives from FDA, and the applicant, may be needed. At the pre-IND/pre-Sub meetings, adequate information on the product will be provided as background to the program, with questions on furthering the development of the compounds being submitted. Informative responses will enable the progression of the product through development.

Please note that there are anticipated regulatory challenges that may affect the development of the product, including adequate safety of the product and adequate characterization of the product and the manufacturing process. When necessary, these aspects will be discussed with the FDA early in the development program to gain agreement on the appropriate level of characterization needed, and input into stability assessments and manufacturing processes.

If the outcomes from the pre-IND or pre-Sub meeting are favorable, an IND or IDE application will be prepared and filed. The PASA resources will provide support for these activities including (but not limited to) the following: (1) gap analysis, (2) regulatory writing and consulting, (3) FDA meetings support, (4) preparation of regulatory documents and FDA communications, (5) pre-IND/pre-Sub briefing packages, (6) preparing, compiling and submitting IND/IDE, (7) preparing annual reports, and (8) Investigator Brochure.

6. SITE STAFF TRAINING

6.1 Overview

To ensure that high-quality data are collected in a manner that assures the safety and protects the rights of study participants, site staffs are expected to undergo training and to demonstrate understanding of training to perform activities specific to their roles on the research teams.

6.2 General Research Training

Site staffs are responsible for completing training required by their institutions to perform research functions. Training may include IRB policies, reporting fraud and abuse, and record retention and destruction policies.

In addition to site specific institutional training, site staffs are expected to complete training in human subjects' protection, Good Clinical Practice, and specimen shipping.

6.2.1 Human Subjects Protection (HSP) Training

All site staffs that have contact with study participants or study data are required to have training in the protection of human subjects as outlined in the Federal Policy for the Protection of Human Subjects or the "Common Rule" published in 1991. The regulations applicable to human subjects' research funded by the Department of Defense (32 CFR Part 219) are designed to ensure minimum standards for the ethical treatment of research participants based on the three principles of ethical research: respect, beneficence, and justice.

Site staffs required to have HSP training include the Principal Investigator, Research Coordinator, Data Manager, and Research Assistant. HSP training must be renewed bi-annually, and new hires must complete HSP training within 30 days. Certificates shall be maintained in a central training file at the site. The site staff will send a list of all staff members and the dates they completed HSP training to the CMC annually, and CMC staff will verify the certificates are in the site central training file during site visits.

Acceptable sources of HSP training include a site's institutional HSP training course, The Collaborative Institutional Training Initiative at the University of Miami (<https://www.citiprogram.org/>) and The NIH Office of Extramural Research (<http://phrp.nihtraining.com>).

6.2.2 Good Clinical Practice Training

GCP is an international standard for research in human subjects developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. In addition to IRB review and informed consent, GCP covers topics on recording data, reporting adverse events, and protocol compliance. Good Clinical Practice is accepted as law in many countries and is the foundation for the laws written by the Food and Drug Administration in the Code of Federal Regulations that govern research in human subjects.

All site staffs required to have HSP training must also have GCP training. GCP training requirements for site staffs are identical to the requirements for HSP training: the training must be renewed biannually, and new hires must complete GCP training within 30 days. Certificates shall be maintained in a central training file at the site. The site staff will send a list of all staff

members and the dates they completed GCP training to the CMC annually, and CMC staff will verify the certificates are in the site central training file during site visits.

Acceptable sources of training include a site's institutional GCP training course or The Collaborative Institutional Training Initiative at the University of Miami (<https://www.citiprogram.org/>).

6.2.3 Specimen Shipping Training

Specimens from human participants and animal subjects, including blood and its components, body parts, and saliva, are considered a Class 6 Hazardous Material. Class 6 Hazardous Materials are poisonous (toxic) and infectious substances and must be handled in compliance with the Department of Transportation regulations. Employees whose job duties include handling hazardous substances must comply with regulations under Title 49 part 172 of the Code of Federal Regulations.

Appropriate specimen shipping training can be obtained through The International Air Transport Association (IATA). IATA is the trade organization for most major airlines and provides training to the general public on shipping procedures and regulations for hazardous materials. Individual institutions may also have training programs that meet all requirements for shipping Class 6 Hazardous Material.

Supervisory site staffs responsible for shipping specimens or designating shipping responsibilities to other staffs must have current Class 6 shipping training. Training certificates must be maintained in the site training files.

6.3 Protocol Specific Training

The CMC will also provide training on protocol implementation and electronic data collection (EDC) system/data management.

6.3.1 Protocol Implementation Training

Protocols conducted within the PASA network may require additional training on study procedures. Testing procedures developed specifically for a single protocol will require training by subject matter experts within and external to the consortium. Most protocol training will be done in a train the trainer model, with the Site Research Coordinator attending the initial training and then training research staffs at their sites.

Protocol training will be coordinated by the CMC and may be conducted in-person or remotely via a webinar depending upon the complexity of the protocol and the equipment required. The determination of mode will be made by the study's Leadership Working Group. All protocol specific training will include training on form completion and data entry. Follow up training will be done via webinar or teleconference as needed depending upon site performance issues or staff turnover. Site staffs will be required to pass certification quizzes to be considered adequately trained.

6.3.2 EDC and Data Management Training

EDC system and data management training will be provided to and required for all site staff involved with data entry. Specific details of EDC and data management training are provided in **Chapter 10**.

7. SITE ACTIVATION

7.1 Overview

Study activation is the process of granting a site approval to begin enrolling study participants into a protocol. There are standard core steps that must be completed for every protocol, and some protocols may require additional procedures that must be followed prior to opening enrollment. Study activation is designed to ensure that sites have the appropriate regulatory approvals, staff training and equipment to conduct the study.

7.2 Protocol Registration

Sites must submit all essential documents to the CMC in a single protocol registration packet with a completed protocol registration cover sheet and checklist. Each protocol will have a protocol registration checklist identifying the documents that should be included in each registration packet with the contents specified in **Appendix A**. At a minimum, the packet will include a copy of the site's IRB approval letter and IRB approved informed consent form. Additional documents in the protocol registration packet may include:

Site Implementation Plan (SIP): a plan that explains in detail how a site will meet requirements for the protocol that are not part of standard study procedures. Examples of nonstandard study procedures include testing that requires a specific model of equipment and specialized training, a data collection schedule that requires staff to be on call, or processing of laboratory specimens that require special handling.

Financial Disclosure Form: a form indicating the amount of stock ownership, speaking fees, or other financial compensation an investigator, and the investigator's spouse and dependents, receives from commercial companies involved in the protocol.

The Statement of Investigator, Form FDA 1572 (1572): an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The 1572 is required for all FDA regulated clinical investigations.

Certificate of Confidentiality: a certificate that protects investigators from being involuntarily compelled by court order or subpoena to disclose sensitive information or identifying characteristics about study participants. Sensitive information includes (but is not limited to) information relating to sexual matters, alcohol and drug use, illegal conduct, mental health, and genetic information or tissue; information that, if released, might be damaging to an individual's financial standing, employability, or reputation within the community. Identifying characteristics include name, address, social security or other identifying number, photographs, genetic information or tissue samples, or any other item or combination of data about a research participant which could lead to identification of that research subject.

Data Use Agreement: a contractual document used for the transfer of data that are nonpublic or otherwise subject to some restrictions on their use. Often these data are a limited data set as defined in HIPAA.

7.2.1 Processing the Protocol Registration Packet

Upon receipt of a protocol registration packet, the CMC will review the documents and compare them to the registration checklist to determine if the packet is complete. If there are

missing or illegible documents, the CMC will put the registration on hold and contact the site staffs. Protocol registration will not be processed until all documents have been submitted.

Upon receipt of a complete registration packet, the CMC review the documents listed below; the documents must meet the requirements noted for approval of the registration. In parallel with the CMC review, the protocol LWG will review the following documents to ensure they meet the requirements listed:

- IRB-Approved Informed Consent Form—proposed changes do not conflict with the protocol
- Site Implementation Plan—the SIP describes adequate preparedness to meet the protocol specific requirements. An inadequate SIP may warrant a site visit by the CMC to determine if the site can conduct the protocol.

The CMC will act as the conduit for communication between the site staff and the PASA leadership for all protocol registration–related issues. The CMC will notify the site staffs of all document revision requests, deadlines, and approval or disapproval notices. The goal of the process is to obtain agreement between the site and its IRB, the protocol LWG, and the CMC leadership on the site’s readiness to enroll subjects. If there is an issue that cannot be resolved, such as language in the consent form mandated by the site’s IRB that the protocol LWG cannot approve, the site will be denied protocol registration and will not be able to enroll participants in the protocol until the issue is resolved.

Upon receipt of the site’s IRB approval in the Protocol Registration packet, the CMC will begin the HRPO submission while the packet is under review.

7.3 Protocol Registration Approval or Disapproval

After HRPO issues an approval the CMC will notify the site staffs of protocol registration status once the CMC and the protocol LWG have made a final determination of approval or disapproval of the registration packet. If registration is denied, the reasons for disapproval will be clearly explained in the written notification. If registration is approved, the expectations for maintaining approval status, such as obtaining IRB annual renewal on time, will be outlined in the written approval notice. Enrollment screens for the protocol will be opened immediately upon issuance of the approval notice.

Please see **Exhibit 2 PASA Protocol Activation** for an overview of the protocol selection, development, and activation process.

7.4 Final Disposition of Protocol Registration Documents

Site staffs are responsible for maintaining all original documents in a central file. The CMC will conduct a brief review of the documents during site visits. The CMC will retain copies of all protocol registration documents and will enter the IRB approval dates in a tracking database to alert the site when annual renewal is due.

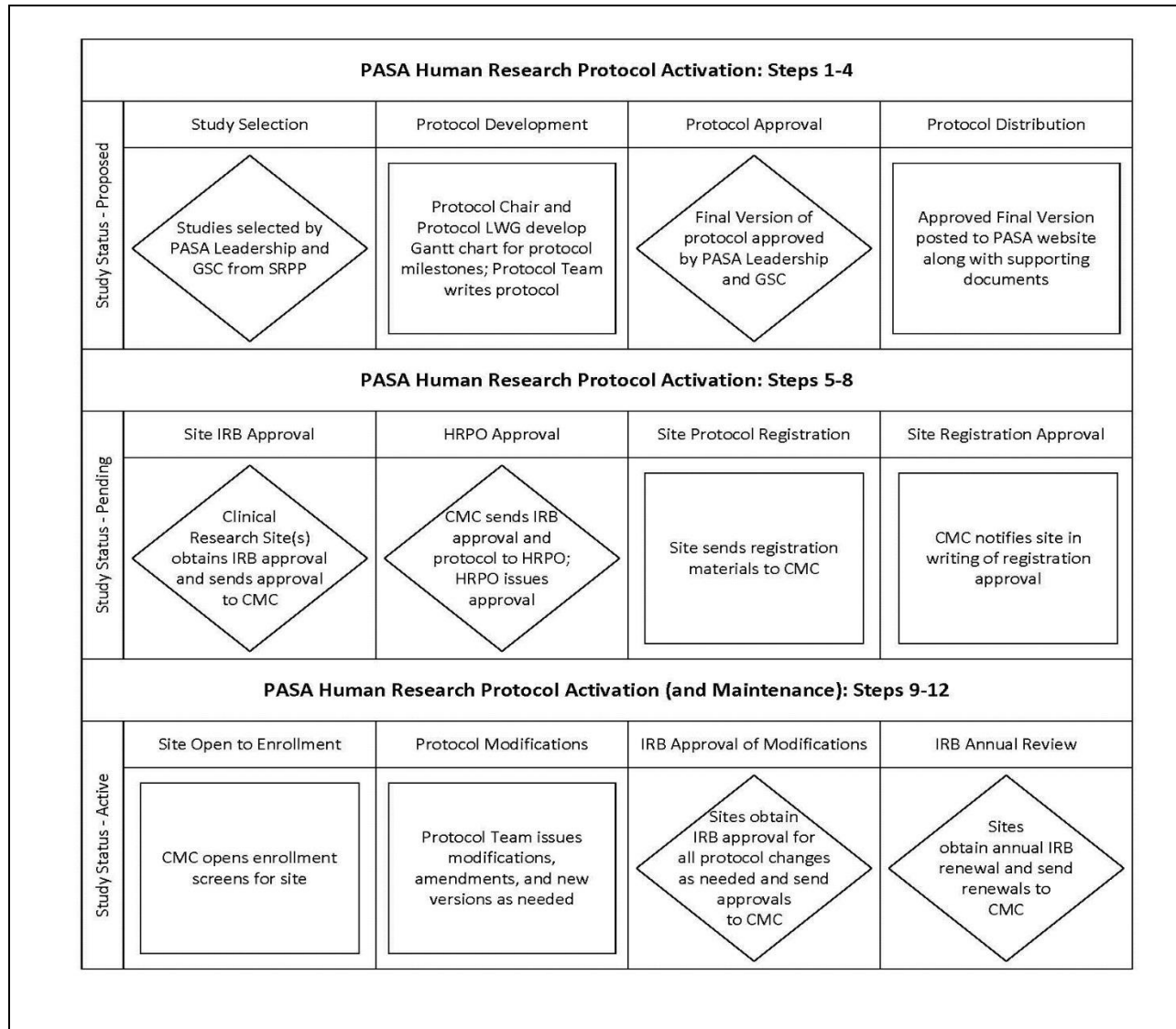


Exhibit 2. PASA Protocol Activation

8. SITE PERFORMANCE MONITORING

8.1 Overview

Site performance monitoring is conducted to ensure that data are of high quality, submitted in time to allow for continuous safety monitoring and to maintain the study enrollment or testing schedule. Site performance monitoring is also important to ensure that network funds are appropriately used.

The CMC and the PASA leadership will monitor site performance in four areas; enrollment and retention, study visit compliance, timeliness for data entry, and the time to resolution of data queries.

8.2 Performance Areas

8.2.1 Enrollment and Retention

Enrollment: For every protocol, the length of the expected enrollment period will be determined based on reasonable monthly/annual targets. Each site participating in the protocol will develop an enrollment plan that will outline monthly and annual target enrollment goals. The individualized enrollment plan allows for variation between sites when evaluating enrollment progress. In general, all sites are expected to contribute an equal number of subjects at a comparable rate unless an alternate protocol enrollment plan is developed in advance. The CMC will track site enrollment daily and provide monthly enrollment reports to the network. If a site is not meeting its enrollment goals over three consecutive months, CMC will hold a conference call with the site staffs and the Protocol LWG to review the enrollment plan and allow the site to discuss the barriers to enrollment. The Protocol LWG will determine if the site's accrual plan will need to be revised to allow for a lower enrollment rate, or if the site will be required to submit a corrective action plan. If the LWG requests a corrective action plan, the site staffs will have 3 months to implement the plan and increase accrual rates. If after 3 months the accrual rates have not improved the site will be placed on probation and the process of administrative separation from the network may begin.

Retention: In addition to adequate accrual, sites will be expected to maintain enrolled subjects on study and minimize dropout rates to the greatest extent possible. The CMC will monitor retention rates every month by tracking the percent of study participants that come off study for reasons other than death and completion of study protocol. Sites will be expected to maintain a specific target percent of enrolled subjects on study. The CMC will hold a conference call with the protocol LWG and sites that cannot maintain the minimum retention rates to discuss the calculation of the rates and the barriers to keeping participants on study. If the low retention is the result of factors beyond the site staff's control (participants get redeployed, or a natural disaster forces participants to move out of the study area) there will be no corrective action required. If the protocol LWG determines the low retention rate is because of staff turnover, or inadequate follow up with participants or other factors within the site's control, the site will be required to submit a corrective action plan. The site will have 3 months to implement the corrective action plan and improve the retention rates. If retention rates do not improve within 3 months the protocol LWG will assess whether or not the site should continue enrolling into the protocol.

8.2.2 Participant Study Visit Compliance

Study participants will be expected to attend a minimum of 90% of their study visits. Site staffs are responsible for ensuring study participants keep study appointments by sending reminders to participants in advance of the visit, accommodating participant needs for transportation and flexible scheduling, and maintaining an atmosphere that encourages participants to remain in the study. The CMC will monitor study visit compliance annually in summary site performance reports. Sites that do not maintain study visit compliance goals will follow the process of conference call, corrective action plan, and probation period outlined above.

8.2.3 Timelines for Data Entry

Site staffs are expected to transfer study data to the database, either by direct data entry or by other transmission, within the timelines established by the protocol. Data which are relevant to participant safety, such as laboratory data collected after study product administration, must be entered in the database within 48 hours. All other study data are to be entered into the study database within 10 business days unless otherwise specified in the protocol. CMC will monitor data entry timeliness on a monthly basis, and sites that are beyond the timeline parameters for three consecutive months will follow the corrective action protocols.

8.2.4 Response Time to Data Queries

Site staffs are expected to respond to data queries issued by the CMC within 10 business days. Examples of data queries include missing data fields, out of range data, or illegible data. Please refer to **Chapter 10** for more details about the data entry and querying process.

8.3 Roles and Responsibilities

8.3.1 CMC

The CMC is responsible for developing enrollment reports and tracking the retention rates, data entry timelines, study visit compliance and response time to data queries. The CMC Data Manager will provide the PASA leadership and Consortium Research Manager (CRM) with routine reports of site performance for review.

The CRM will require the site staffs to identify the cause of the problem and to develop a corrective action plan. The CRM will then review the corrective action plan and either approve the plan or request corrections, and will monitor the performance of the site for improvement over a three month period.

8.3.2 Consortium Leadership

The Consortium Leadership is responsible for determining the course of action if a site does not meet enrollment or performance goals. If necessary, the Consortium Leaders may place a site on temporary suspension or begin the process of administrative separation from the network.

In the event administrative separation is initiated, RTI International will terminate the subcontract by first providing written notice to the appropriate party's Contact within 30 days. The details of the discontinuation process are described in Attachments 3A & 3B of the subcontract documents. RTI International will pay termination costs as allowable under OMB Circular A-21 or A-122 or 45 CFR Part 74 Appendix E, "Principles for Determining Costs

Applicable to Research and Development under Grants and Contracts with Hospitals" as applicable.

RTI International will notify the government funding institutions and the GSC of the intent to separate a subcontract prior to initiating the process, and will provide written notice of the separation once the process is complete.

9. SUBCONTRACT MANAGEMENT

9.1 Issuing Subcontracts

RTI will issue subcontracts in collaboration with the Office of Proposal, Project & Procurement Services that is responsible for RTI's proposal and contract management. Each subcontract will define a clear Scope of Work with measurable performance standards and desired outcomes. The scope of work may include performance milestones which can be tied to payments. Subcontracts include all applicable Federal terms and conditions that must be flowed down. Subcontracts also include line item budgets by year. Budgets and scopes of work will be reviewed and approved by RTI prior to subcontract award. Changes to all subcontracts that result in substantive changes to the budget, including major modifications of sub-awards and changes across cost categories, require approval from USAMRAA and are subject to recommendations by the GOR at CDMRP prior to USAMRAA approval.

PRIOR WRITTEN approval of the RTI Subcontract Administrator is required for obtaining services of consultants and lower-tier subcontractors. Costs for consultants and lower-tier subcontracts who have not received PRIOR WRITTEN approval will not be reimbursed. Inclusion in the Subcontractor's budget or proposal does not constitute request or approval of consultants or lower-tier Subcontractors.

When requesting the use of consultants, the Subcontractor shall furnish information concerning the need for such services, the consultant rate of pay, number of hours or days needed, reasonableness of the fees or costs, a copy of the proposed consulting agreement/subcontract, and any additional information required to make a determination of acceptability.

When requesting the use of lower-tier subcontracts, Subcontractor shall follow the requirements set forth in FAR 52.244-2 (Subcontracts). Cost-plus-a-percentage-of-cost subcontracts or purchase orders are prohibited.

9.2 Billing and Reporting

Subcontractors should invoice RTI monthly. RTI is responsible for ensuring that progress is being made on the project, and that invoices are in line with actual effort expended. Subcontractors are to provide monthly progress reports that details currently ongoing activities and work or activities that have been completed. RTI will review submitted invoices and monthly progress reports for proper documentation and to verify effort. Once approved, the payment will be made within 30 days.

9.3 Performance Monitoring

RTI monitors subcontract performance on multiple levels. In addition to the monthly progress reports mentioned in Section 4.2, we will have regular communication with subcontractors for continued performance management. The type and timing of communication varies depending on the type of subcontract. At a minimum, meetings will take place on a monthly basis, but can be scheduled as frequently as needed to monitor performance.

When a subcontractor's performance is unsatisfactory, RTI can take several steps to rectify the situation. First, we will raise concerns with the leadership group overseeing the subcontractor and let the group know we will also have discussions with the Consortium Steering Committee or Consortium Leadership Team as required. If needed, we can schedule biweekly or weekly meetings to encourage a subcontractor to focus on successfully meeting

goals. RTI staff can arrange site visits to work directly with subcontractors when needed. Additionally, RTI will communicate with the Government Steering Committee regarding subcontractor performance and can leverage the influence of the GSC.

9.4 Subcontract Termination

RTI may terminate a subcontract award in whole or in part, at any time, as described in Article 33 of subcontract documents. Additional causes for termination are related to bankruptcy, financial insolvency, or similar, as described in Article 33 of subcontract documents.

10. DATA MANAGEMENT

10.1 Overview

This chapter provides a high-level overview of the major aspects of data management for the PASA consortium, and includes a description of general information technology systems, electronic data capture systems and processes, and study management processes. This chapter will be supplemented by study-specific information technology (IT) and data management guidelines where necessary.

The sections that follow provide a detailed overview of the general IT systems that will be used to manage all aspects of study operations, including: study management tools that will be used to track various aspects of study development and deployment, such as IRB status and site readiness; general IT systems that will be used to communication purposes; and many aspects of the electronic data capture systems and processes.

10.1.1 IT Systems

The PASA web portal (<https://pasa.rti.org/>) will be the central hub for all project operations, and will contain a series of web applications used to manage various aspects of consortium operations. All consortium members will be given access to the secure private side of the portal via username and password, and access to all resources in the site will be carefully controlled using role-based security. In addition to being a secure repository for all consortium documentation, the web portal's document management capabilities will largely negate the need to exchange documents by e-mail. It is the policy of the PASA consortium that e-mail exchange of documents should be limited, to the extent possible, for operational and security reasons. Other applications within the web portal include: a consortium wide directory and user account management, mailing list and study group management, site IRB and study readiness tracking, consortium wide announcements, data integration, and research study reporting. In addition, the PASA consortium portal is tightly integrated with our primary EDC system: Medidata Rave. These systems and associated processes are described in detail below.

10.1.2 Roles and Responsibilities

The following table summarizes the roles of the key Biostatistics, Data Management and Study Management (CMC) core staff from both a consortium level and study level perspective.

Exhibit 3. Consortium Management Core (CMC) staff

Role	Responsibilities
Clinical Research Manager	<p>The CRM is the primary point of contact for research sites for any issues relating to study conduct, or for any clinical issues. Where necessary the study coordinator will involve other team members to resolve a problem. The primary responsibilities of the CRM are:</p> <ul style="list-style-type: none"> • Management of the protocol and case report form development processes • Primary point of contact for research sites for operational issues (e.g., IRB processing, clinical issues, protocol clarification issues) • Coordination of study-specific meetings • Protocol implementation training

(continued)

Exhibit 3. Biostatistics, Data Management and Study Management (CMC) Core Staff (continued)

Role	Responsibilities
Data Manager	<p>The data manager works in collaboration with the CRM and other team members to manage all aspects of the data collection process, which includes providing training and guidance on the EDC system, and related data entry processes. The primary responsibilities of the data manager are:</p> <ul style="list-style-type: none"> • Assisting with case report form development • Primary point of contact for data issues, system issues and data queries • Managing data system updates • Data system training • Data cleaning and locking
IT Systems Lead	<p>The IT systems lead provides oversight for all systems development activities including the web portal, the EDC system, and any data integration processes. The primary responsibilities of the IT systems lead are:</p> <ul style="list-style-type: none"> • Managing all aspects of system development and programming • Primary point of contact for web portal issues that are not related to a specific study • Web portal training • User account management and data security
Study Statistician	<p>The study statistician works with the research coordinator and the data manager to ensure that the protocol has enough statistical power to address the research question. The primary responsibilities of the study statistician are:</p> <ul style="list-style-type: none"> • Statistical design for the study protocol • Study safety reporting oversight • Collaborating with the PI to resolve statistical issues

The staff roles listed above are the primary operational data management staff roles for the consortium and study. When necessary, issues or questions will be escalated to the Consortium Director, Associate Consortium directors, lead statistician, lead coordinator, or data management director. The names and roles of all staff are clearly delineated in the consortium directory, available in the PASA consortium web portal.

10.1.3 IT Security

Ensuring high standards of security is a responsibility shared by all members of the consortium. All IT and data systems have been developed using industry-standard security practices and up-to-date software systems; IT security systems and processes are fully compliant with the necessary VA and DoD standards, in addition to complying with appropriate data privacy standards for human subjects protection. The PASA CMC Core has obtained additional approval from the VA Privacy and Security Officers at the Office of Clinical Science Research and Development to ensure the plans for data protection are adequate. Although the security aspects of the PASA IT systems are fully documented in an associated IT Security Plan, this section provides some basic operational guidance. All consortium members should:

- Use a strong password for all accounts (i.e., the web portal and the EDC system), keep their password secret and change their password periodically

- Be cognizant of the information communicated in e-mail, and ensure that only non-identifying information is sent via e-mail (sending subject-identifying information to the coordinating center is an IRB infraction)
- Log out of all web resources when work is complete
- Reporting any security issues to the PASA coordinating center (pasa-techsupport@rtiresearch.org)

The PASA web portal provides centralized user account management. The CMC will create user accounts for consortium members, provide guidance on portal use, and review all accounts and ensure that staffs are assigned the appropriate levels of access.

10.2 Study Management Tools

The PASA web portal will provide a series of study management tools that will support end to end study management and include: site approval and IRB tracking, study progress monitoring (including site capitation monitoring) and reporting, document management and communication tools for study development, study reporting, and electronic data capture and management.

10.2.1 Site Approvals and IRB Tracking

Site readiness for study startup and IRB approval status is tracked through the PASA web portal. Site coordinators will be asked to upload evidence of IRB approval, the system will automatically track the IRB expiration date, and status reports will be available to the coordinating center and to the research sites. Status is tracked by protocol and protocol version. Additional site readiness requirements will be study specific and will therefore be described in detail in the appropriate study manual of procedures. Issues with site approvals or IRB status should be directed in the first instance to the CMC study coordinator.

10.2.2 Study Progress Monitoring and Reporting

There will be a dedicated section of the web portal for each study, whether it is in development, open to enrollment, closed to enrollment with subjects on study, or completed. The main home page for each active study will contain a detailed summary of study status, which will include:

- A table of enrollment numbers by site
- A graphical (bar graph) summary of enrollment by site
- A line graph of enrollment rate with expected enrollment shown
- For randomized trials, a line graph of current and expected randomization rate
- Other graphical data summaries appropriate to the specific study

In addition, detailed study metrics will be available on the study reporting page. Other study management tools available in the web portal include:

- Subject visit tracking dashboard
- Subject and visit specific case report forms in PDF format

10.2.3 Document Management, Communication, and Calendaring

The PASA web portal is the primary communication tool for the network and as such contains sophisticated document management and list serve capabilities. Document management capabilities include the ability to upload documents, track versions, and send links by e-mail. In addition, the PASA list serves are closely linked to the web site security roles: providing users access to a specific role or group (such as a protocol development team), will automatically allow them access to the appropriate resources in the web portal and also add them to the appropriate list serve. Communication with the various PASA groups (e.g., LWGs) can be achieved by sending an e-mail to the appropriate list serve group. All groups have the form PASA-xxx-yyy@rtiresearch.org where xxx is the group classification (e.g., lwg, and yyy is the name of the group: neuroimaging). In this example the full e-mail address would be PASA-lwg-neuroimaging@rti.org and any e-mail sent to this address would be received by all members of the Neuroimaging LWG.

The master PASA calendar, located in the web portal, will list all scheduled meetings, provide links to meeting resources, and provide call-in or webinar information. The PASA calendaring system is tightly integrated with Microsoft Outlook, so meeting invitations will be synchronized automatically to ensure that any changes to meeting schedules are automatically reflected both on the web calendar and on individuals' Outlook calendars.

10.3 Electronic Data Capture

Primary electronic data capture for the PASA will be performed using Medidata Rave, which is an industry-standard cloud-based EDC system. Data are hosted securely on servers provided and maintained by Medidata. In addition to ensuring high standards of uptime and performance, Medidata is compliant with all applicable IT security standards. This section describes our processes and procedures for providing access to the EDC system, gives an overview of required training, describes data entry procedures and expectations, and technical support procedures.

10.3.1 System and Study Access Procedures

EDC system access is determined on a study by study basis for a given consortium member. Access to an individual study is managed by the data manager, and may require an individual to provide documentation of appropriate protocol training, site IRB approval, or other requirements. Upon launch of a study, the data manager will work with the lead coordinator at each site to determine which staff members at the site require access, to ensure that all necessary requirements have been met and determine the appropriate role and level of access for each staff member. Once necessary approvals have been confirmed, automated system e-mails will be sent to invite users to join the study. All users will have to complete a series of eLearning activities prior to gaining study access.

10.3.2 Data Entry Procedures and Expectations

Medidata Rave is an easy-to-use web-based EDC system that allows users to authenticate (log-in), select a subject and visit, and enter data for that visit. The system provides real-time edit checks to ensure that data meet any necessary criteria. Site performance, which includes timely data entry and resolution of queries, is discussed in more detail in Chapter 9, however minimum requirements for timeliness of data entry are:

- Lab data entered into the appropriate system within 28 hours
- All clinical data entered in Medidata Rave within 10 business days

- Queries answered or resolved within 10 business days

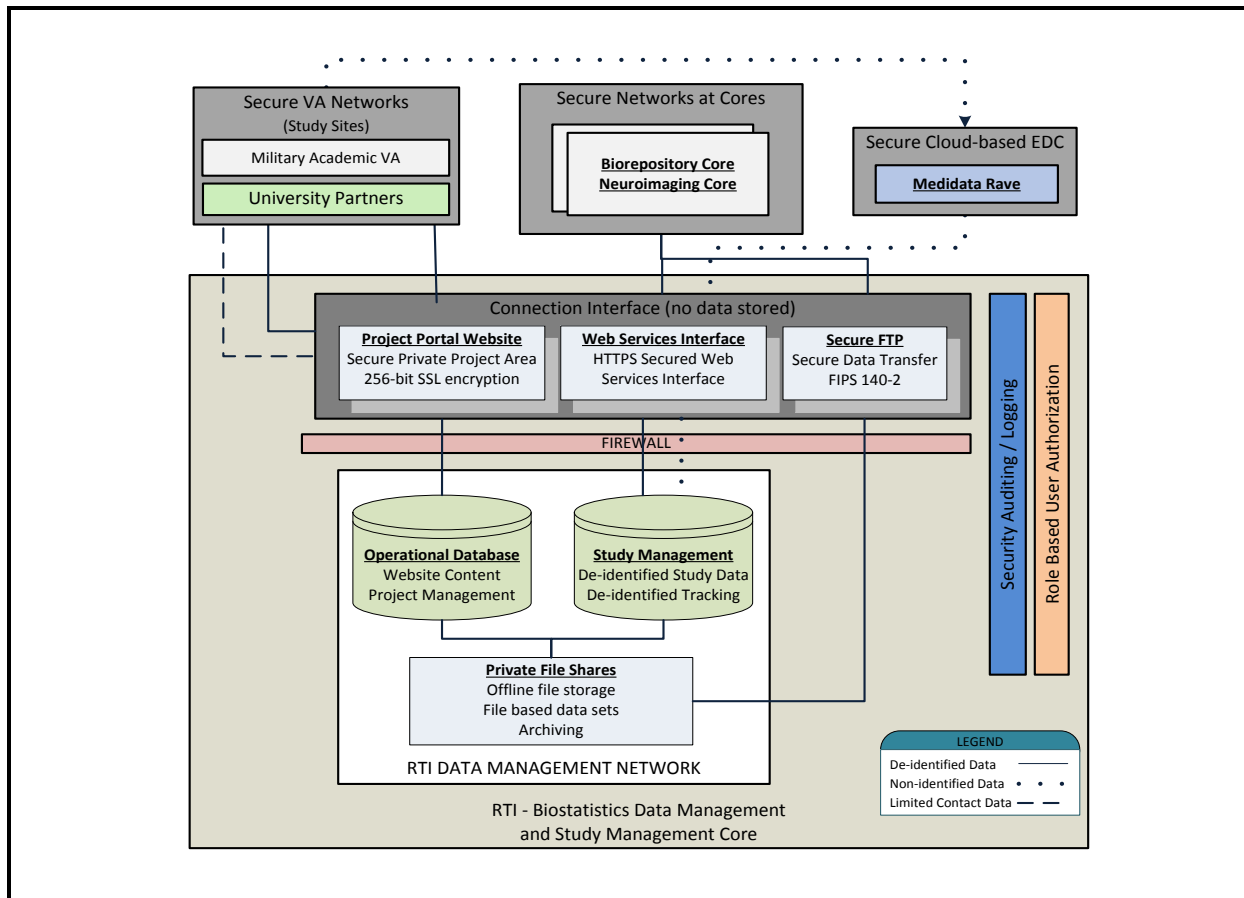
10.3.3 Technical Support

While Medidata provides technical support and users are free to contact them to retrieve passwords, we have found that most issues involve some aspects of the protocol design or implementation, so we request that all questions initially be directed to the data management team (PASA-dm@rtiresearch.org).

10.4 Data Integration

This section provides a brief overview of the data sources that will be used on the PASA. In addition to clinical data collected with Medidata Rave, we will also be collecting Neuroimaging data and Biospecimen data. For these data sources there will generally be two components: (1) artifact tracking information (e.g., the shipment of specimens); and, (2) derived data or measurements. The diagram below summarizes the general data flow from these sources to the data center.

Exhibit 4. PASA System Security Architecture



Additional details of the data flow for neuroimaging data and biospecimen data are described below.

10.4.1 Neuroimaging Data Collection

Neuroimaging will be performed at the research sites and the resulting dicom files will be transmitted directly to the Neuroimaging core via their secure infrastructure and transfer protocols. If electronic transmission is not possible, and images must be shipped by mail, site staff will need to track their shipments to the Neuroimaging core. Similarly, neuroimaging core staff will need to track receipt of images. Once established, these procedures will be described in a separate neuroimaging standard operating procedure. Regardless of method (electronic transfer or shipping) used to transfer MRI images, tracking of MRI completion will be performed via summary data captured via case report form at the time of image acquisition. These summary details will be keyed into Medidata.

10.4.2 Biospecimen Collection

As with neuroimaging data, the specific procedures for the tracking and shipment of specimens and the integration with the biospecimen core are still being developed. However, at a minimum tracking of specimen collection will be accomplished by completing the appropriate case report form in Medidata Rave. Entry of data into Medidata will then generate an automatic communication to the biospecimen core to expect a shipment. Further details of these procedures will be described in a separate biospecimen standard operating procedure.

10.4.3 Common Data Elements for TBI

The DoD requires that awardees make TBI data generated via this award mechanism available to the research community by depositing de-identified research data into the Federal Interagency TBI Research (FITBIR) Informatics System on a quarterly basis. The FITBIR Informatics system is a free resource to the research community designed to accelerate comparative effectiveness research on brain injury diagnosis and treatment. Data reporting to FITBIR is an opportunity for investigators to facilitate their own research and to collaborate with others doing similar research. FITBIR guidance and policies, as well as the considerable advantages of FITBIR use to the researcher, are detailed at FITBIR: Federal Interagency Traumatic Brain Injury Research Informatics System <http://fitbir.nih.gov/>. FITBIR allows for de-identification and storage of data (medical imaging clinical assessment, environmental and behavioral history, etc.) of various types (text, numeric, image, time series, etc.). Use of FITBIR's Global Unique Identifier system facilitates repeated and multi-user access to data without the need to personally identify data sources. FITBIR encourages collaboration between laboratories, as well as interconnectivity with other informatics platforms. Such community-wide sharing requires common data definitions and standards.

Data elements must be reported using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (CDEs) or entered into the FITBIR data dictionary as new, unique data elements. For the most current version of the NINDS TBI CDEs, go to <http://www.commondataelements.ninds.nih.gov>. Assistance will be available to help the researchers map their study variables to specific CDEs and ensure the formats of the CDEs collected are compatible with the FITBIR informatics system. If the proposed research data cannot be entered in CDE format, the investigators must supply a proposal for an alternative data submission or data sharing vehicle and justification for use. Use of the TBI CDEs is required wherever possible in an effort to create standardized definitions and guidelines about the kinds of data to collect and the data collection methods that should be used in clinical studies of TBI.

10.5 Data Queries and Query Resolution

Medidata Rave provides a real-time querying system that facilitates simple and complex edit checks both within and across case report forms. Examples include simple numeric range checks to complex comparisons across multiple forms. When required criteria are not met, affected data items are flagged in Rave and research staff must address the issues. The process for addressing queries in Rave is described below and will be covered in detail at the aforementioned training sessions.

10.5.1 Query Process

Queries occur in Rave for multiple reasons including the entry of data is not compliant with protocol requirements, data are missing, or complex cross form checks have highlighted potential inconsistencies. In addition, as part of their review the data manager may enter manual queries in the system. In all cases, data fields with queries are highlighted in red in the system. Queries can generally be addressed in two ways: (1) by corrected the affected data so that it is compliant, or (2) by answering the query. If the data are corrected and become compliant with protocol requirements, the query will resolve itself and disappear. In this case, no further action is required. If the data are not available, or are, in fact correct, site staff may submit an answer to the query. An answer to a query is a message explaining why the data element is correct. This answer will be reviewed by the data manager, and if they are in agreement, the query will be closed manually. Note that queries will not automatically close if both of these methods are used. If you have the correct data, please do not enter an answer.

10.5.2 Data Manager Responsibilities

The data manager is the primary point of contact for all EDC system issues. In addition the data manager will review a site's subjects on a regular basis. If issues or inconsistencies are found the data manager will communicate with the site, either through the built-in querying system or by e-mail if appropriate, to ensure that all issues are resolved in a timely manner. Although protocol specific questions should be directed to the study coordinator, the data manager can be helpful in understanding how data should be entered into the EDC system. The data manager will also routinely review the EDC system for missing forms, and will generate periodically a missing forms report to site staff.

10.5.3 Expectations for Query Resolution and Timing

Expectations for query resolution and timing were discussed in **Section 8.3.2**. In addition, it is important the site staff develop a dialog with the data manager to ensure the smooth operation of the study as the data manager can be a useful resource for many aspects of the study.

10.5.4 Query Reports

A number of query reports are available in Medidata Rave. These will be described in detail in the study training and include:

- query summary report
- query detail report
- query timing report

Additional reports will be available through the PASA web portal.

11. STUDY MONITORING

11.1 Study Progress and Safety Monitoring Plan

All studies or clinical trials which include human participants conducted by the PASA consortium must have a Study Progress and Safety Monitoring Plan (SPSMP) approved by the GSC before trial initiation. For pre-clinical studies, details of study progress and safety monitoring will be specified within the protocol or the study's manual of procedures.

For human subjects' research, the SPSMP that will be created typically contains details that are in addition to content found in the relevant sections of the protocol or manual of procedures document for the study. However, if all necessary study monitoring details are included in the protocol or manual of procedures, a separate SPSMP document is not required. All PASA consortium funded or sponsored research must have a study progress and safety review at least once a year for as long as participants continue on study follow-up.

The SPSMP specifies:

- The designated reviewer(s)/review committee for each type of report.
- The schedule for submission to reviewer(s)/review committees for each type of report.
- The types of study progress and safety monitoring reports may include:
 - Periodic study progress and safety monitoring reports for review by the study team (usually with no study arm-specific data)
 - Interim monitoring reports for review by independent study monitoring committees (includes study arm-specific data as applicable)
 - Periodic study progress and safety reports for review by designated individual study safety monitors (may include study arm-specific data as determined by the SPSMP)
- The contents of each report type, including the key parameters for assessment of study progress, feasibility (including actual vs. expected accrual, participant losses, and event evaluability), timeliness and quality of data submission, safety, futility, efficacy, and other outcomes, as appropriate.

The characteristics of a SPSMP are determined by the type of clinical trial to be monitored. The intensity of monitoring will primarily depend on the complexity, population, and risks involved with the study. For example, clinical trials of an investigational product must have very frequent and detailed monitoring of safety parameters in comparison observational studies. A pre-specified plan for interim statistical analysis, including any necessary statistical adjustments for interim evaluations, is a required component of the SPSMP for interventional studies.

11.2 Reporting

A written summary of the results of each independent interim monitoring review by the DMC must be submitted to the GSC within 30 days after completion of the study progress and safety review. At minimum, these reports will be provided to the GSC at the frequency of each review as specified in the SPSMP.

In addition, once a safety monitoring mechanism is established for a trial, each of the relevant IRBs will be informed of the operating procedures with regard to study progress and safety monitoring (who, what, when, and how monitoring will take place). This information will serve to assure the IRB that the safety of the research participants is appropriately monitored. If the IRB is not satisfied with the monitoring procedures, it should request modifications. IRB comments should be considered seriously and all attempts will be taken to satisfy IRB requests.

The GSC, with the assistance of the PASA Consortium Coordinating Center, will distribute a summary report of DMC reviews to all participating investigators for submission to IRBs.

12. CLINICAL SITE MONITORING

12.1 Overview

The purpose of site monitoring is to ensure that site facilities and record-keeping practices are adequate for the conduct of PASA protocols. Staff from the CMC will conduct site monitoring. Informed consent forms will be reviewed during monitoring visits to ensure that all participants have given informed consent to participate in the study.

Most site monitoring visits will occur annually and may be conducted in-person or remotely depending upon the risk of noncompliance as determined by the Clinical Research Manager. More frequent visits may be conducted if requested by the GSC, or if required by the risk level of the study. The number of charts, extent of chart review, and data items to be verified will be determined on a protocol by protocol basis. As appropriate, the CMC will develop a monitoring plan for circulation to the site(s).

12.2 Roles and Responsibilities

12.2.1 CMC

The CMC is responsible for initiating the visit scheduling, conducting the visit, reporting findings to the staff at the end of the visit, developing a written report of the visit for distribution to the study site and the PASA leadership, and reporting serious findings to PASA leadership immediately.

12.2.2 Clinical Sites

The clinical sites are responsible for providing mutually agreeable dates for the site monitoring visit, providing workspace for the monitor, providing staff members who can assist the monitor in retrieving study records, resolving issues during the monitoring visit when possible, and responding to the written monitoring report after it is distributed.

12.3 Scheduling Monitoring Visits

The CMC will contact the site PI and Study Coordinator to schedule the visit at least 6 weeks in advance. Study monitoring visits will last a minimum of 1 day and, depending on the level of review required, may take up to 4 days.

The CMC will send a confirmation letter to the site PI outlining the dates, an agenda, and objectives two weeks before the monitoring visit. The objectives of the visit will be clearly outlined in the confirmation letter. Visit objectives will, at a minimum, include informed consent review, participant chart review for source data verification, and site facility review. Additional objectives may include a review of staff training records, regulatory files, and a laboratory or pharmacy visit.

A random sample of participant files will be reviewed during each visit. The letter will include a list of 50% of the files that will be reviewed during the visit. The monitor will provide the site staff with the remaining 50% of the participant IDs upon arrival at the site.

12.4 Monitoring Visit Activities

The CMC monitor will meet with the site PI and Study Coordinator on the first day of the visit and review the agenda and purpose of the visit. The site PI is required to be present at the initial meeting and at the debriefing at the end of the monitoring visit. The Study Coordinator or

designee is required to be available throughout the visit to respond to the monitor's questions and to assist with the retrieval of study records. At the end of the visit, the monitor will schedule a debriefing meeting to provide a summary of the findings and recommendations that will be noted in the written report.

12.5 Monitoring Visit Reports

Within 10 business days after the last day of the visit, the monitor will distribute a written site monitoring report to the clinical site, PASA leadership, and the CDMRP GOR for distribution to the GSC. The report will summarize the activities of the monitoring visit, including the findings and recommendations.

12.6 Follow-Up to Monitoring Visits

Clinical site staffs may respond to visit reports in writing to either confirm or contest the monitor's findings. If there are serious findings that the PASA leadership determine warrant a compulsory response, the response must include an explanation of the problem and a corrective action plan, and be submitted to the CMC within 21 business days of the last day of the monitoring visit.

13. QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Overview

Quality assurance (QA) and quality control (QC) are activities critical to the success of the PASA. Quality assurance is a forward-looking process aimed at preventing errors and is best implemented through the development of standard operating procedures and this Manual of Operations. Quality control is a real-time process that examines the work produced before it is released to determine if there are flaws or defects created as a result of errors in production. Quality control is implemented on the PASA through data review checks and data monitoring activities, for example. All entities involved in the PASA are responsible for QA and QC activities within their purview. The purpose of this chapter is to provide a high level overview of the QA process, and to outline the requirements for clinical quality control plans at the research sites.

13.2 Quality Assurance—Planning

The best practice for quality assurance involves careful planning at the beginning of an activity. For any specific deliverable or goal, no matter how large or small, Project or Task Leaders will determine the best way to approach the task and the most efficient way to convey important information to the project members, project staff, and other relevant stake holders. The activities at each stage of development are:

- define and document how the project or task will be managed;
- gather and document the project requirements;
- develop the deliverable to meet requirements; and
- review the deliverable to verify requirements have been met.

13.2.1 Developing the Project Plan

Developing the project plan is the first step in defining and documenting how the task will be managed. The steps for developing the project plan are:

1. Write a general plan for conducting the work;
2. Establish and document the project organizational chart; and
3. Draft a roles and responsibilities matrix.

13.2.2 Create Work Breakdown Structure (WBS)

Gathering and documenting the project requirements are done through the creation of a WBS. The WBS identifies all the tasks for the project and continually breaks them down until they are at the lowest level. The WBS is updated throughout the lifecycle of the project.

13.2.3 Developing the Deliverable

In the development of the deliverable, the task requirements are translated into the product. The development phase includes analysis and design, testing activities, and may include iteration back to requirements, documentation, and management activities. This phase ends after the Project Team has produced, reviewed, and approved the product.

13.2.4 Verifying Requirements

After a product or deliverable has been completed, the Project or Task Leader then compares the finished product to the initial requirements outlined in the project plan. If the product does not match the requirements, the team will either revise the product, or if requirement changes were made that were not reflected in the project plan, revise the project requirements documentation using the project's established change procedure.

13.3 Quality Control—Clinical Quality Management

The purpose of the clinical quality control activities is to ensure that the rights and safety of participants are protected and that data collected are accurate and complete. Since extensive external monitoring on the PASA is not feasible, clinical research sites are encouraged to develop, implement and evaluate a Clinical Quality Management Plan (CQMP) that focuses on QC activities. QC activities will assure compliance with applicable regulatory requirements, identify areas in need of corrective action, verify data accuracy, and assure a constant state of readiness for an external audit or monitoring visit.

QC is the real-time, ongoing (day-to-day) operational techniques and activities that are undertaken to verify the requirements for quality trial-related activities. The CQMP should describe the person(s) responsible for the development, implementation, and evaluation of the CQMP and the person(s) responsible for performing the QC activities.

At a minimum, the following key indicators should be included (as applicable) for QC review:

- Informed consent form and process
- Eligibility criteria
- Scheduled tests and procedures
- Missed visits, tests, or procedures
- Concomitant/prohibited medications
- Study product administration/dosing
- Clinical endpoint identification
- Identification and reporting of SAEs and AEs

The CQMP should also include a description of QC activities, including the scope (number and type) of QC activities. QC is typically performed on 100% of Case Report Forms (CRFs) prior to entry into the database and on other trial related forms. For example: Verification that all headers, required fields, and dates are completed correctly on CRFs.

Description of tools or checklists to be used in the QC processes should also be identified in the CQMP. Examples may include, but are not limited to, the following: visit reminder checklists; data entry, query and error reports from the data management center; clinical site monitoring reports; and chart review tools.

Documentation of QC activities should include the following:

- Name of the reviewer

- Date of the review
- Participant identification numbers of items reviewed where indicated
- Specific items that were reviewed
- Time period covered by the review
- Findings/results of review
- Tools for QC activities will be provided by the CMC.

14. STUDY CLOSE-OUT

14.1 Overview

This chapter outlines the administrative procedures associated with study completion. Closeout activities verify that study procedures have been completed, data collected, and if relevant, study intervention is returned to the responsible party or prepared for destruction.

Closeout may be:

- **Routine**—in preparation for the completion of a study, or
- **Unscheduled**—as a result of failure to obtain continuation funding, negative or positive findings, findings in other studies that affect the study under review, or other unforeseen events (e.g., safety concerns). Unscheduled close-out processes will follow the same steps listed below, although the timeframe for completion of these activities may be abbreviated.

If the study is a randomized, double-blind clinical trial, the plan should include actions to unblind/unmask and debrief site staff and subjects upon trial completion. The study close-out plan should be reviewed and approved by the safety monitoring group (Data Monitoring Committee).

14.2 Study Close-Out Process

The CMC and Clinical Research Sites will coordinate the close out process to ensure the following tasks are completed.

14.2.1 Study Forms

- All outstanding CRFs have been corrected, collected, organized, and filed as required.
- All data queries are corrected and resolved.
- All SAEs have been reported to the DSMB (or Safety Monitor), sponsor, IRB, and other organizations, as specified in the protocol.
- All adverse events and SAEs are recorded and followed up to resolution in accordance with procedures detailed in the protocol.

14.2.2 Study Files

- The investigator's study files are complete and up-to-date with originals of the following maintained in the Study Binder, as relevant:
 - Investigators' Curriculum Vitae(s) (CVs), Investigator's Brochure(s)
 - IRB approval letters for the protocol, all amendments, Informed Consents, annual reviews and advertisements (including updated approvals)
 - IRB membership list
 - All IRB correspondence
 - All Coordinating Center and site correspondence

- Site signature log
 - Drug accountability records documenting the investigational product received, dispensed and returned or destroyed
 - Copy of randomization code for randomization, if applicable
- All informed consents are signed and on file.
- Record retention procedures are in place and conform to protocol or institutional requirements, whichever is longer (type and length of retention, consequences of improper record retention).
- Indication of any study materials which will be shredded.
- Individual to contact for study files.

14.2.3 Clinical Supplies

- Clinical supplies, including any treatment intervention materials, have been shipped or disposed of according to protocol directions.
- As relevant, drug accountability records (shipping, receipt, dispensing, return or destruction) are up to date.

14.2.4 Laboratory Records and Specimen Retention

- Laboratory records are complete and up to date (reference ranges, laboratory certifications, specimen tracking records, specimen storage records).
- A plan for storage/retention of samples and maintenance of patient confidentiality is in place.
- Study specimens have been shipped to the biorepository.

14.2.5 Final Reports and Equipment Removal

A final report has been prepared (or will be prepared) for the IRB and in conformance with institutional reporting requirements. The report is likely to include, but is not limited to, study conduct and outcome, pertinent safety and efficacy observations, complete disclosure of any SAEs experienced during the course of the study, and the study close-out date.

- An announcement on the study outcomes for submission to the PASA, including a report on study progress, has been prepared by Investigator.
- Arrangements for the removal and shipment of any study specific equipment received by the site (e.g., computers, diagnostic equipment, and participant monitoring devices) have been made.

14.2.6 Participant Rights and Notifications

A letter to thank each study participant has been prepared that includes the following information, as relevant:

- Study findings

- Treatment assignment
- Explanation of reason for close-out
- Treatment options: whether continued treatment with the assigned medication is indicated, and how and where treatment may be obtained
- Transfer of care responsibilities
- Rights to confidentiality, privacy, and to no further contact from study staff, it that is participant's preference
- Subsequent updates or recalls if new and important information emerges following separation
- As relevant and depending on publication status, a copy of the first study article, or a copy of the letter should be included in the participant's file.

15. PUBLICATION, PRESENTATION, AND INFORMATION DISSEMINATION PROCEDURES

Consortium members share the goals of rapid analysis and publication of study data and equitable attribution for all investigators.

The PASA Publications Committee is responsible for overseeing its implementation and for dispute resolution. The objectives of the policy are to:

- Encourage the accurate and objective development of scientific manuscripts or presentations based on work conducted by the PASA Consortium;
- Ensure and expedite the timely publication and presentation of all pertinent PASA Consortium findings to the scientific community;
- Prevent overlap of content across papers, and ensure investigators adhere to the aims outlined in their submission concept;
- Ensure that all investigators, particularly those of junior rank, have the opportunity to participate and be recognized in Consortium papers;
- Ensure that the PASA leadership are able to carry out the timely review of PASA publications and presentations; and
- Maintain and post a current and complete list of PASA publications and abstracts.

15.1 Concept Development and Writing Team Identification

All presentations and publication concepts are voted on and prioritized by the Publication Committee in collaboration with PASA Leadership. Progress in developing an abstract or manuscript will be tracked by the PASA leadership and reported at each GSC meeting.

Presentation and publications based on primary and secondary outcome results proposed by a project are determined in advance for each study. The Lead Study Investigator(s) is (are) responsible for outlining potential submissions based on the primary and secondary aims of the study (i.e., pre-planned analyses).

Any PASA Investigator may propose additional publications or presentations based on data analyses not pre-specified in the study protocol (i.e., ad-hoc analyses). Proposals based on single study data are reviewed for practicability by the study's lead biostatistician prior to submission. Proposals based on data from two or more Consortium studies are reviewed by the lead biostatistician with the more/most relevant expertise. Proposals must be submitted to the CMC at least 12 weeks prior to abstract, presentation or manuscript submission deadlines (ideally sooner for manuscripts). The proposal must include approval by the assigned biostatistician. The CMC distributes the submission to the Publications Committee, which provides a response within one week. Approval is granted for non-duplicative submissions unless a majority of the members of the Publications Committee object. In the case of duplicative submissions, the Publications Committee may recommend support for one submission or that the investigators work collaboratively. The selection of one submission is based on majority vote by the Committee.

Each presentation or publication will have an established writing team and writing team Chair. For presentation and publications based on pre-planned analyses for a study,

assignment of the Chair is made based on consensus of the Study Protocol Team. If consensus cannot be reached, primary responsibility is determined by the Publications Committee based on equitability. For ad-hoc analyses, the Chair will typically be the PASA Investigator submitting the concept, or will be determined by the submitting Investigator. If an investigator needs to abdicate Chair responsibility, the responsibility is reassigned using the same process. The writing committee for pre-planned analyses will generally include at minimum representatives from each site participating in the study and the PASA CMC. The writing committee for ad-hoc analyses will be determined by the submitting Investigator and will vary depending on the content of the intended analyses.

15.2 Writing Team Chair

The Writing Team Chair is the first and corresponding author except under unusual circumstances which need to be approved in advance by the Publications Committee.

The writing team Chair is responsible for:

- ensuring all writing team authors have approved the communications to the Publication Committee, PASA Leadership and GSC;
- ensuring the CMC has verified the statistical analysis and results;
- verifying that terms and definitions are consistent with those published in clinical.trials.gov;
- ensuring disclosures are obtained/COI are resolved; (this task may be delegated to the CMC coordinator of the study; the CMC will store all original disclosures/COI forms);
- monitoring the level of contribution from each Writing Team member;
- including a statement of the journal's policy on disclosure on an early manuscript draft;
- updating the Publication Committee of the composition of the writing team;
- settling conflicts regarding authorship;
- obtaining a signed copy of the authorship forms required by the journal from all authors on the Writing Team; (this task may be delegated to the CMC coordinator; the CMC will store all original authorship forms. The Writing Team Chair may keep copies at his/her site. In addition, for archiving, the Writing Team Chair will send photocopies or electronic files of the final submitted manuscript to the CMC);
- for manuscript: notifying the Chair of the Publications committee 2 weeks before submission of an abstract or manuscript to the publications committee;
- corresponding with the journal with support from the Writing Team and the CMC as necessary;
- initiating the PMCID and completing process;
- preparing a layman's summary posting on the website after manuscript acceptance;

- developing a set of talking points for accepted primary/index papers for use by other PASA investigators;
- preparing a letter to participating subjects for mailing once the primary paper is published; and
- working with the PASA Leadership or other Institutes on press releases and other types of communication.

15.3 Ensuring Rapid Data Publication and Presentation

A Consortium priority is the rapid publication and presentation of study results in high quality peer reviewed journals and venues. The CMC maintains a list of all abstracts and manuscripts involving data derived from Consortium studies.

15.3.1 Abstracts

Abstracts (for professional meetings, etc.) are sent to the CMC a minimum of two weeks prior to submission deadlines. The abstract must include approvals by the (1) writing team Chair; (2) Lead Biostatistician; and (3) coauthors. The CMC distributes the proposed submission to the Publications Committee, which provides a response within one week to permit timely submission(s). The writing team Chair sends a copy of accepted abstracts to the CMC for posting and archival.

If the primary paper for a study has not yet been published, all data presented at scientific meetings will need prior approval of the PASA leadership in addition to the Publications Committee before results may be released and are embargoed for the date/times of scientific presentation or an official PASA announcement, whichever occurs first.

15.3.2 Manuscripts

The writing team Chair coordinates the writing of the manuscript and revision(s) based on input from all coauthors. After all coauthors approve the manuscript, the writing team Chair (or designee) sends the manuscript to the CMC for distribution and approval by the Publications Committee.

The Publication LWG does not conduct a scientific review of the manuscript but confirms adherence to the publication policy and appropriate acknowledgement of the Consortium. Drafts are reviewed with the following objectives in mind:

- to ensure that no publication will have a deleterious effect on the Consortium process, on Consortium study acceptance, or on the interpretation of Consortium study results;
- to correct factual and conceptual inaccuracies;
- to safeguard the rights of Consortium study subjects;
- to ensure that the work of Consortium Investigators and study staff are appropriately recognized; and
- to inform the GSC, Consortium Investigators, and the Advisory Committees of all public dissemination of information.

Before submission to a journal (publication venue), every manuscript must receive approval by the (1) writing team Chair; (2) Lead Biostatistician; and (3) coauthors. Additional approvals may be required based on the PASA Leadership's discretion. For example, manuscripts based on ad-hoc analyses of one or more PASA studies may require the approval of an original Lead Study Investigator and study statistician.

One copy of each paper shall be submitted to the Grant Officer representative (GOR) simultaneously with its submission for publication. Copies of all publications resulting from the research shall be forwarded to the USAMRAA Grants Officer or Grants Specialist as they become available, even though publication may in fact occur subsequent to the termination date of the award.

Within two weeks of the paper being published, the writing team Chair forwards a copy to the CMC which distributes copies of the reprinted article to all co-authors and places a copy in the Consortium archive.

Responsible Investigators should complete the manuscript in a timely fashion. If 3 months have passed between final analysis and first draft or 6 months have passed between final analysis and submission and an extension has not been requested or granted, the PASA Leadership, in consultation with the Publications Committee, may reassign the manuscript to another appropriate investigator.

Copies of manuscripts or subsequent reprints resulting from the research shall be submitted to usarmy.detrick.medcom-cdmrp.mbx.cdmrp-reporting@mail.mil.

15.4 Authorship and Credits

The PASA Consortium adheres to the International Committee of Medical Journal Editors (ICMJE) guidelines (www.icmje.org) in determining authorship eligibility of a given manuscript. Authorship and author order in a manuscript is discussed early in the development process and the following are taken into consideration: (1) overall workload contribution; (2) intellectual contribution; and (3) patient accrual at the site(s), in that sequence. In most circumstances, the writing committee Chair is typically the first author. In the case of the primary aims, this is the Lead Investigator or his/her designee. For preplanned study analyses, first authorship positions are ordinarily granted to all Co-Lead Investigators; the Lead Biostatistician is typically the next author; and at least one individual from each participating site is commonly included as author. The writing committee Chair is also afforded the discretion to recommend that additional authors be named, based on their contributions to the work and in keeping with ICMJE guidelines.

The last "author," in most circumstances (journal/meeting specifications permitting), is the "Pharmacotherapies for Alcohol and Substance Abuse Consortium." According to the ICMJE (<http://www.icmje.org/index.html#author>), "When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments Section. Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under such headings as "clinical investigators" or "participating investigators," and their function or contribution should be described—for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

As detailed in section 7.2, it is the responsibility of the writing team Chair to properly credit the appropriate co-authors and to acknowledge all other contributors (along with their

specific role[s]) in the Acknowledgments section. The writing team Chair also obtains written permission from each contributor named as such in the article; the CMC can help obtain these permissions. Each author is responsible for obtaining any appropriate clearances from his/her site or institution.

All publications and abstracts using PASA data or having PASA support for any of the authors' contributions to the manuscript must include the statements below, as applicable. "Information" includes, but is not limited to, news releases, articles, manuscripts, brochures, advertisements, still and motion pictures, speeches, trade association meetings, and symposia.

- a. "The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office" and;
- b. "This work was supported by the Office of the Assistant Secretary of Defense for Health Affairs through the Alcohol and Substance Abuse Research Program under Award No. W81XWH-15-2-0077. Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the Department of Defense."
- c. "In conducting research using animals, the investigator(s) adhered to the laws of the United States and regulations of the Department of Agriculture." W81XWH-15-2-0077
- d. "In the conduct of research utilizing recombinant DNA, the investigator adhered to NIH Guidelines for research involving recombinant DNA molecules." (<http://www.nih.gov>)
- e. "In the conduct of research involving hazardous organisms or toxins, the investigator adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories." (<http://www.cdc.gov/biosafety>)

15.5 Dispute Resolution

In the unlikely event publication disputes (e.g., timeliness of submission; choice of target journal) or authorship (e.g., order of authorship; membership of author list) that is not remedied through thoughtful discussion among the involved parties, the Publications Committee will act as a mediating body. If a dispute directly involves a member of the Publications Committee, that individual recuses him- or herself from the deliberations (other than to represent their own claim in the dispute).

If a Consortium investigator is not satisfied with the remedy prescribed by the Publications Committee in its mediating role, he/she has the right to request engagement at the next level of dispute resolution. This involves participation by the PASA leadership to provide a final decision, resolving the dispute.

Any dispute arising out of or relating to Project Intellectual Property will be referred to the investigators' respective officers, as outlined in the individual intellectual property agreements. Such officers will attempt to resolve the dispute(s) by informal means, taking into consideration the project objectives, the terms and conditions of the Award, and applicable law. If the designated officers are unable to resolve the dispute(s) within 30 days the investigators must agree to settle the dispute in a court of competent jurisdiction upon filing of a legal action by the aggrieved party. During the pendency of the dispute, the aggrieved party shall perform diligently within the performance of the scope of work and in accordance with the terms and conditions of the sub agreement.

15.6 Publication Involving a Third Party

As a courtesy to sponsoring/collaborating organizations and as a safeguard for proprietary information, Consortium members participating in clinical studies consult with their sponsors prior to publishing study results. Consultation provides sponsors the opportunity to review the publication to request that the organization's confidential information be removed, or to delay the publication to allow filing of any patentable inventions. This period of delay does not exceed 30 calendar days, unless there are extenuating circumstances, and is considered on a case-by-case basis by the Publications Committee.

Prior to release to the public, the writing team Chair must notify the USAMRAA Grants Officer and the GOR of the following: planned news releases, planned publicity, advertising material concerning grant/cooperative agreement work, and planned presentations to scientific meetings. This provision is not intended to restrict dissemination of research information; the purpose is to inform the USAMRMC of planned public release of information on USAMRMC-funded research, to adequately respond to inquiries and to be alert to the possibility of inadvertent release of information which could be taken out of context.

15.7 Disclosure of Financial Interests in Publications

In scholarly publications, all authors must disclose their related financial interests in accordance with the ICMJE (www.icmje.org) guidelines. It is the writing committee Chair's responsibility to ensure that all authors provide this information. However, neither the Publications Committee nor the writing committee Chair is in a position to verify the accuracy of the disclosures. It is, therefore, incumbent on authors to regulate themselves. Should it come to the attention of the Publications Committee that information provided is disingenuous, the journal is notified and disciplinary action is taken against the offender(s). The nature of the disciplinary action is determined by the Publications Committee in consultation with the PASA leadership.

15.8 Intellectual Property Management

The PASA Leadership has established an Intellectual Property Management Plan that governs the management and disposition of intellectual property generated under the PASA award. The provisions of the Plan apply to all consultants, subcontractors, students, or other individuals employed for the purposes of the PASA award. The objectives of the Plan include (1) promoting the patenting, licensing, and rapid commercialization of intellectual property developed under the Award, and (2) promoting the rapid dissemination of scientific data for the public good.

"Intellectual Property" specifically means patents, trademarks, copyrights, protected data, and other forms of comparable property protected by Federal law and foreign counterparts covering data first produced, inventions first conceived, or inventions first conceived or actually reduced to practice in the performance of Award Work. "Confidential Information" means any data, specifications, samples, materials, research information, new product development initiatives, business plans, and business objectives, which are proprietary and confidential.

PASA leadership must be informed in writing of any inventions developed under this award. Except to the extent provided in a separate agreement, each Participant shall retain title to Subject Inventions and other Project Intellectual Property developed exclusively by its employees and agents, subject to any applicable Government rights.

Except to the extent provided in a separate agreement, participants shall have equal ownership interests in Project Intellectual Property to the extent that it is developed jointly by the Participants. In cases of joint Project Intellectual Property, the Participants with an ownership interest agree to negotiate and enter into a future interinstitutional agreement allowing one Participant to take the lead in Project Intellectual Property protection and commercial licensing of the joint Project Intellectual Property.

15.8.1 Intellectual Property Licensing

Participants who retain title to Project Intellectual Property may grant exclusive or non-exclusive licenses for use of Project Intellectual Property. Unless otherwise agreed in writing, joint owners of Project Intellectual Property will share equally in paying patenting and licensing expenses, and any benefits received from licensing (i.e. royalties and equity) will be distributed equally between co-owners. Except to the extent specifically prohibited in an inter-institutional or other agreement between parties, all licenses will permit private or public domestic educational or nonprofit research institutions to use Project Intellectual Property on a royalty-free basis for research and education, but not for commercial purposes, subject to confidentiality requirements.

All licenses will comply with and conform to the terms and conditions of the Award and incorporate the applicable Government rights and requirements. Licensing of Project Intellectual Property will not inhibit or impede the performance of Award Work.

15.8.2 Government Rights in Subject Inventions

Pursuant to 15 U.S.C. § 3710a b(1)(A) the Government will have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced any Subject Inventions throughout the world by or on behalf of the Government for research or other Government purposes.

15.8.3 Ownership and Control of Technical Data and Materials

Except to the extent provided in a separate agreement, each Participant will have the right to use other Participants' technical data for the sole purpose of carrying out Award Work. Each Participant will establish and implement specific measures and protocol to protect such data from disclosure. Data and animal and human research samples and materials that are generated by a Participant under the Award (collectively, the "Materials") are owned by the Participant. Participants will use reasonable efforts to share Materials with other Participants for the purposes of the Award and according to applicable policies for each Participant. Absent agreement to the contrary, Participants may not transfer ownership of Materials to a party that is not a Participant without the written consent of a majority of Participants. If a Participant is no longer party to the Consortium, such Participant agrees to transfer Materials to another Participant so that such Materials can continue to be used for the purposes of the Award.

15.8.4 Confidentiality

Each Participant agrees to accept in strict confidence any and all Confidential Information made available to it by the disclosing Participant and which is designated by the disclosing Participant as proprietary and confidential. For a period of five (5) years after the disclosure of Confidential Information the receiving Participant shall not disclose Confidential Information to any third party, directly or indirectly, without first obtaining the written consent of the disclosing Participant. Limitations of confidentiality obligations will be outlined in individual intellectual property agreements.

16. PASA DATA AND SAFETY MONITORING BOARD

16.1 Overview

The DSMB will be an independent advisory group responsible for monitoring the data quality and participant safety for all clinical trials conducted by the PASA Consortium. The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, assuring data quality and integrity, and for monitoring the overall enrollment of each study. Recommendations made by the DSMB regarding PASA clinical trials will be provided to the GSC who will have final authority concerning all recommendations.

16.2 Membership

The PASA leadership is responsible for determining the appropriate composition of the DSMB and also identifying qualified individuals to serve on the board. The GSC will provide formal approval of both the composition and proposed members of the board. At a minimum, the DSMB will include a Chairperson, clinical experts, an ethicist or community advocate, and a statistician. If needed, additional members with specific expertise may be added to the board to review certain trials.

Potential DSMB members will be identified by the PASA leadership via a nomination process. Specifically potential candidates will be solicited from the PASA leadership, the GSC and participating clinical investigators of the network. All nominees will be assessed by the PASA leadership or their designees for interest, available time, appropriate expertise and lack of conflicts of interest and a final list of candidates will be provided to the GSC for review and approval prior to formalizing the committee.

16.3 Charter

The PASA leadership will draft a charter that will guide the DSMB in its operations and responsibilities. The charter will be reviewed and approved by both the GSC and the DSMB. The charter will be completed prior to finalization of the study protocol for any PASA conducted clinical trial. The charter will detail responsibilities and composition of the DSMB; communication between the DSMB and any other PASA entities (e.g., GSC, PASA leadership, clinical investigators); conflicts of interest, scheduling, organization, and logistics of meetings; voting rules; and anticipated content of study reports submitted to the DSMB and DSMB recommendation letters.

Appendix A PASA Protocol Registration Checklist

NOTE—This form is required for all materials submitted to the CMC

Section 1: Fill in all applicable information below			
1) Date of Submission:		2) Total number of Pages (including cover):	
3) Clinical Research Site Names:			
4a) PASA Protocol Name:		4b) Final Protocol Version Number:	
5) Name of Site PI:		Telephone Number:	
		E-mail address:	
7) Name of Study Coordinator:		Telephone Number:	
		E-mail address:	
8) Additional Contact(s) that should receive notifications:		Telephone Number:	
		E-mail address:	
Section 2: Check one box below that describes the reason for submission			
<input type="checkbox"/>	Initial Registration	<input type="checkbox"/>	Corrected Materials: <input type="checkbox"/> Response to Registration with Required Corrections <input type="checkbox"/> Disapproval Notification
<input type="checkbox"/>	Full Version Protocol Amendment Registration	<input type="checkbox"/>	Change of Site Investigator Request
<input type="checkbox"/>	Letter of Amendment (LoA) Registration	<input type="checkbox"/>	Continuing/Annual Review
<input type="checkbox"/>	Requested Materials in Response to a Requested Materials Notification from the CMC	<input type="checkbox"/>	Updated 1572
<input type="checkbox"/>	Disapproval Reversal Request	<input type="checkbox"/>	Other Submissions (specify below exactly what is being submitted & for what type of processing):

CMC at RTI
For Questions e-mail: pasa@rti.org

Appendix B

PASA Consortium—List of Essential Documents

1572—for the Principal Investigator and Sub-Investigators. All versions of form 1572 sent to the FDA should be in this folder.

Correspondence—all relevant study correspondence including protocol questions, study concerns, etc.

CVs—for the Principal Investigator and Sub-Investigators. CVs should be signed, dated, and updated every 2 years to verify that the information is accurate and current.

DSMB—copy of all DSMB reports.

Financial Disclosure Forms—for the Principal Investigator and Sub-Investigators. Signed and dated copy of Form FDA 3455.

Investigator Brochure

ICF (Informed Consent Documents)—original copies of all IRB approved versions (evident by the IRB approval/validation stamp) with version dates or numbers.

IRB Compliance—

- Federal Wide Assurance number (FWA#)—Printed copy of Institution's FWA Information from OHRP website
- List of IRB Members—*this is required to determine that the site PI or Site Sub-I were not on the board that reviewed the protocol.* Documentation from the IRB chair indicating the PI/SUB-I was not part of the review is sufficient if IRB does not want to supply a list of members.

IRB Reviews—all materials related to IRB approvals and reviews including:

- Original Approval letters or notification of IRB decisions
- Copy of investigator response to IRB notification (if applicable)
- Approved/validated recruitment materials
- Approved/validated additional study information distributed to participants
- Any translated study materials
- Serious Adverse Events submitted to the IRB
- Protocol violations submitted to the IRB
- Safety memos submitted to the IRB
- Annual Renewals
- Additional IRB correspondence

Laboratory—includes CLIA Certification, FACT certification from MD Anderson and CAP certifications.

License Medical—for the Principal Investigator and Sub-Investigators. Please monitor licensure expiration dates so that those nearing expiration can be promptly replaced.

License Other—valid licenses/certification for all professional study staff. This can include nursing licensure if study coordinator will be monitoring the patient after infusion; certifications for assessments requiring training, etc.

Log Delegation—should include the investigator and sub-investigator(s), study coordinator(s) and all other clinic staff who routinely see study subjects and who have specific data collection/interpretation/management responsibilities. New or replacement staff should be added as appropriate.

Log Screening—track and document all subjects screened for the study.

Log Site Monitoring—track and document any review of the study, such as outside monitoring visits from sponsor and FDA site visits/audits.

Log Staff—of all key personnel, their signature and initials. New or replacement staff should be added as appropriate.

Sponsor Authorization—the sponsor will provide authorization for each site to begin study recruitment.

Technical Memos—memos that document changes to the protocol; EDC system or CRF modifications.

Training HSP (Human Subject Protection Training)—required for all professional study staff; certificate must be current within 3 years.

Training Other—certificates or equivalent of training for the following items:*

- Study Protocol
- Electronic Data Capture (Medidata RAVE)

* Must be cross-matched to delegation log to ensure all staffs are trained according to role.

Appendix B

Intellectual Property Management Plan

CONSORTIUM INTELLECTUAL PROPERTY MANAGEMENT PLAN

I. Preamble

1. Research Triangle Institute, d/b/a RTI International (“RTI”) has received an award from the Department of Defense, via the U.S. Army Medical Research and Materiel Command (“USAMRMC”) and U.S. Army Medical Research Acquisition Activity (“USAMRAA”), as part of the Pharmacotherapies for Alcohol and Substance Abuse (“PASA”) Consortium. This Consortium is initially composed of the following research institutions (individually referred to as a “Consortium Party” and collectively referred to as the “Consortium Parties”):

- a. Research Triangle Institute, d/b/a RTI International (“RTI”)
- b. The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (“HJF”), on its own behalf and on behalf of Uniformed Services University of the Health Sciences (“USUHS”); and
- c. The Baylor College of Medicine (“BCM”)

This Intellectual Property Management Plan (the “Plan”) is established by the Consortium to govern the management and disposition of intellectual property arising out of or resulting from Award Work.

2. The Plan

- a. This Plan is applicable only to matters directly funded by and directly relating to the Award and the Subaward referred to in the preamble above and to extensions and additional phases of the Award or Subaward.
- b. The provisions of this Plan apply to Consortium Parties, and may apply to any consultants, subcontractors, students, independent contractors, or other individuals employed by any of the Consortium Parties for the purposes of the Award or the Subaward, provided that these individuals have agreed in writing to be bound by the terms of this Plan.
- c. The general purpose of the Plan is to address the protection and disposition of Intellectual Property developed under the Award and Subaward, within the framework of federal intellectual property laws, regulations, and policies. To the extent that this Plan may conflict in any way with the provisions of the Award, in particular, the intellectual property provisions contained therein, the Award provisions take precedence.
- d. The Plan objectives include:
 - i. Promoting the patenting, licensing, and rapid commercialization of Project Intellectual Property developed under the Award and Subaward, and
 - ii. Promoting the rapid dissemination of scientific data for the public good.

3. Authority

- a. As a federal agency, USAMRMC and USAMRAA are entering into this Plan through Executive Order 10096, as implemented in 37 C.F.R. §§ 501-501.11 and 15 USC 3710a et seq.

b. New members may be added to the Consortium with the approval of the Government Steering Committee under its usual and customary procedures.

II. Definitions

1. "Award" refers to Pharmacotherapies for Alcohol and Substance Abuse Consortium funding under Prime Award No. W81XWH-14-ASARP-CA and any continued funding from the Department of Defense for a similar purpose.

2. "Award Work" means all work that is directly funded by the Award and performed by Consortium Parties and arises out of the technical milestones, deliverables, and other project objectives specifically described in the Award.

3. "Government Steering Committee" or "GSC" means the group composed of members designated by the Congressional Directed Medical Research Programs (CDMPR).

5. "Project Intellectual Property" means intellectual property (specifically, patents, trademarks, copyrights, mask works, protected data, and other forms of comparable property protected by Federal law and foreign counterparts) that is directly funded by the Award and developed in the performance of Award Work.

6. "Subject Invention" means any invention that is directly funded by the Award and developed in the performance of Award Work.

7. "Confidential Information" means any data, specifications, samples, materials, research information, new product development initiatives, business plans, and business objectives, which is proprietary, and confidential.

III. Title to Subject Inventions and Other Project Intellectual Property

1. The Parties will promptly inform PASA in writing of any Subject Invention upon receipt of an invention disclosure describing such Subject Invention by their technology transfer offices or offices with equivalent or similar functions. Upon written request and on an annual basis, PASA shall provide a summary of Subject Inventions reported under this Plan.

All invention disclosure notifications should be sent to:

Doreen Collins
RTI International
3040 Cornwallis Road
Research Triangle Park, NC 27709
dcollins@rti.org

2. With respect to intellectual property rights, and the disposition thereof, this Plan will be subject to the terms of any agreement pertaining to specific projects or studies under the Award.

3. Except to the extent provided in a separate agreement, each Consortium Party shall retain title to Subject Inventions and other Project Intellectual Property developed exclusively by its employees and agents, subject to any applicable Government rights.

4. Except to the extent provided in a separate agreement, Consortium Parties shall have equal and undivided ownership interests in Project Intellectual Property to the extent that it is developed jointly by the Consortium Parties. In cases of joint Project Intellectual Property, the Consortium Parties with an ownership interest agree to negotiate and enter into a future interinstitutional agreement allowing one Consortium Party to take the lead in Project Intellectual Property protection and commercial licensing of said joint Project Intellectual Property.

IV. Intellectual Property Licensing

1. Consortium Parties who retain title to Project Intellectual Property may grant exclusive or non-exclusive licenses for use of Project Intellectual Property, subject to the terms of this Plan and any inter-institutional agreement signed thereafter. In case of a joint invention, the sharing of patenting and licensing expenses and any benefits received from licensing (i.e. royalties and equity) shall be determined by the joint owners of Project Intellectual Property in an inter-institutional agreement on a case-by-case basis with such sharing dependent upon the proportional contribution of the Consortium Parties to the development of the joint invention.

2. Except to the extent specifically prohibited in an inter-institutional or other agreement between Consortium Parties, all options or licenses granted to non-Consortium parties shall include without limitation, provisions to permit private or public domestic educational or non-profit research institutions to use Project Intellectual Property on a royalty-free basis for research and education, but not for commercial purposes, subject to confidentiality requirements.

3. All licenses shall comply with and conform to the terms and conditions of the Award and incorporate the applicable Government rights and requirements. Licensing of Project Intellectual Property shall not inhibit or impede the performance of Award Work.

4. Government Rights in Subject Inventions. Pursuant to 15 U.S.C. § 3710a b(1)(A) the Government shall have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced any Subject Inventions throughout the world by or on behalf of the Government for research or other Government purposes.

V. Ownership and Control of Technical Data and Materials

1. Except to the extent provided in a separate agreement, each Consortium Party shall have the right to use other Consortium Parties' technical data for the sole purpose of carrying out Award Work. Data and animal and human research samples and materials that are generated by a Consortium Party under the Award (collectively, the "Materials") shall be owned by such Consortium Party. Materials jointly generated by more than one Consortium Parties shall be jointly owned by such co-generating Consortium Parties. A Consortium Party or Parties shall share Materials with other Consortium Parties for the purposes of conducting research under the Award. Absent agreement to the contrary, Consortium Parties may not transfer ownership of Materials to a third party without the written consent of the GSC, provided that a Consortium Party may transfer and/or license Materials solely owned by such Consortium Party to any party either inside or outside the Consortium, subject to the terms herein. If a Consortium Party leaves the Consortium, upon request, such Consortium Party agrees to transfer Materials to another Consortium Party so that such Materials can continue to be used for the purposes of the Award.

VI. Confidentiality

1. Each Consortium Party agrees to accept in strict confidence any and all Confidential Information disclosed orally and/or in writing, by the disclosing Consortium Party respecting the Confidential Information and which is designated, either on its face or in a separate writing provided by the disclosing Consortium Party to the receiving Consortium Party within ten (10) days of any non-written disclosure, by the disclosing Consortium Party, as proprietary and confidential. For a period of five (5) years after the disclosure of Confidential Information to a receiving Consortium Party, the receiving Consortium Party shall not disclose Confidential Information to any third party, directly or indirectly, without first obtaining the written consent of the disclosing Consortium Party.

VII. Limitations of Confidentiality Obligations

1. The confidentiality obligations outlined in this Plan shall not be binding on each receiving Consortium Party with respect to any Confidential Information which:

- a. is rightfully in the possession of the receiving Consortium Party at the time of disclosures;
- b. is or becomes known to the public generally through no fault or other action of the receiving Consortium Party;
- c. is obtained lawfully by the receiving Consortium Party on a non-confidential basis from a third party;
- d. is developed by the employees, agents, or representatives of the receiving Consortium Party independently and as a result of its own efforts, without the use of, or access to, the Confidential Information received from the disclosing Consortium Party, as evidenced by written records
- e. Information that is required to be disclosed by a Consortium Party to a government authority or by order of a court of competent jurisdiction; provided, however, that reasonable advance notice is given to the non-disclosing Consortium Party and the disclosing Consortium Party takes reasonable good-faith actions to limit the scope of the Confidential Information required to be disclosed.

VIII. Dispute Resolution

1. Any dispute between Consortium Parties, arising out of or relating to Project Intellectual Property or the interpretation of this Plan, shall be referred to the Consortium Parties' respective officers, as designated below. Such officers shall attempt to resolve the dispute(s) by informal means, taking into consideration the project objectives, the terms and conditions of the Award, and applicable law.

The designated officers are as follows:

For BCM: Leanne Scott, Ph.D., Director, Sponsored Programs

For HJF: Elizabeth Folk, Vice President, Sponsored Programs and Acquisitions

For USUHS:

For RTI: Dean T. Woodward, Asst. General Counsel

For ____: _____

For ____: _____

If the designated officers are unable to resolve the dispute(s) within 30 days after service of a written notification of the dispute(s), the Consortium Parties agree to settle the dispute in a court of competent jurisdiction upon filing of a legal action by the aggrieved party. During the pendency of the dispute, the aggrieved party shall perform diligently within the performance of the scope of work and in accordance with the terms and conditions of the subagreement.

IN WITNESS THEREOF, the Parties hereto have executed and approved this Intellectual Property Management Plan on the dates below their signatures. By signing below, the lead principal investigator for each Consortium Party asserts that they have read and understood this Plan. Additional Parties to this Plan may be added with the written consent of RTI and by also signing below.

AGREED:

RESEARCH TRIANGLE INSTITUTE

By: _____

Name: _____

Title: _____

Date: _____

BAYLOR COLLEGE OF MEDICINE

By: _____

Name: _____

Title: _____

Date: _____

**HENRY M. JACKSON FOUNDATION FOR THE
ADVANCEMENT OF MILITARY MEDICINE, INC.**

By: _____

Name: _____

Title: _____

Date: _____

By: _____

Name: _____

Title: _____

Date: _____